EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2021
EMA/CHMP/21349/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BroPair Spiromax

International non-proprietary name: salmeterol / fluticasone propionate

Procedure No. EMEA/H/C/005591/0000

Note

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

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List of abbreviations

%CV	Percent Coefficient of Variation
%RE	Relative Error
ABS	Acrylonitrile Butadiene Styrene
ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
AHR	Airway Hyper Responsiveness
API	Active Pharmaceutical Ingredient
APSD	Aerodynamic Particle Size Distribution
AQLQ(S)	Asthma Quality of Life Questionnaire with Standardised Activities
ARIA	Allergic Rhinitis in Asthma
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine Triphosphate
AUC0-12h	Area Under the Plasma Concentration-Time Curve from Time 0 to 12 Hours After Study Drug Administration
AUC0-30min	Area Under the Plasma Concentration-Time Curve from Time 0 to 30 Minutes Post-Dose
AUC0-t	Area Under the Plasma Concentration-Time Curve from Time 0 to the Time of The Last Measurable Drug Concentration
BALF	Bronchioalveolar Lavage Fluid
BDP	Beclomethasone Dipropionate
Bid	Twice Daily
BU	Blend Uniformity
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum Observed Plasma Concentration
CNS	Central Nervous System
CoA	Certificate of Analysis
COPD	Chronic Obstructive Pulmonary Disease
CRS	Chemical Reference Substance
CSR	Clinical Study Report
CTD	Common Technical Document
Cyclic AMP	Cyclic-3',5'-Adenosine Monophosphate
CYP	Cytochrome P450 Isozyme
DCU	Dose Content Uniformity
DCU-TL	Dose Content Uniformity Through Life

DMF	Drug Master File = Active Substance Master File
DOM	Date of Manufacture
DPI	Dry Powder Inhaler
DSC	Differential Scanning Calorimetry
e.g.	Example Given
ECD	Electrochemical Detection
ECG	Electrocardiogram
ED50	Median Effective Dose
EDMF	European Drug Master File
EDQM	European Directorate for The Quality of Medicines and Healthcare
EEA	European Economic Area
EMA	European Medicines Agency
EP	European Pharmacopoeia
EPAR	European Public Assessment Report
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEF25-75	Forced Expiratory Flow Between 25% And 75% Of the Forced Vital Capacity
FEV1	Forced Expiratory Volume In 1 Second
FEV1 AUEC0-12h	Area Under the Effect Curve for Forced Expiratory Volume In 1 Second from Time 0 To 12 Hours Postdose
Fp or FP	Fluticasone Propionate
Fp MDPI	Fluticasone Propionate Multidose Dry Powder Inhaler
FPD	Fine Particle Dose
FS	Fluticasone Propionate/Salmeterol Xinafoate
FS MDPI	Fluticasone Propionate/Salmeterol Xinafoate Multidose Dry Powder Inhaler
FT-IR	Fourier Transmission Infra-Red (Spectroscopy)
FVC	Forced Vital Capacity
GC	Gas Chromatography
GERD	Gastro-oesophageal Reflux Disease
GINA	Global Strategy for Asthma Management and Prevention Global Initiative For Asthma
GLP	Good Laboratory Practice
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GR	Glucocorticoid Receptors
HC	Health Canada
HCMC	Human Cultured Mast Cells
HCP	Healthcare Professional
HFA	Hydrofluoroalkane
HLT	High Level Team

HNA	1-Hydroxy-2-Naphthoic Acid
HPA	Hypothalamic-Pituitary-Adrenal
HPA axis	Hypothalamic–Pituitary–Adrenal Axis
HPLC	High Performance Liquid Chromatography
i.e.	Id Est (Engl: That Means)
i.v.	Intravenous
IC50	Median Inhibitory Concentration
ICH	International Conference on Harmonisation
ICP	Inductively Coupled Plasma
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
INN	International Non-Proprietary Name
IPC	In-Process Control Test
IR	Infra-Red
ISAAC	International Study of Asthma and Allergy in Childhood
ITT	Intent-To-Treat
KF	Karl Fischer
LABA	Long-Acting Beta2-Agonist
LC-MS/MS	Liquid Chromatography-Tandem-Mass Spectrometry
LLOQ	Lower Limit of Quantification
LOD	Loss on Drying /Limit of Detection
LOQ	Limit of Quantitation
LS	Least Squares
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDI	Metered-Dose Inhaler
MDPI	Multi-Dose Dry Powder Inhaler
MHRA	Medicines and Healthcare Products Regulatory Agency
MMAD	Mass Median Aerodynamic Diameter
MO	Major Objection
MPA	Medicinal Products Agency
MS	Mass Spectroscopy
NDA	New Drug Application
NDS	New Drug Submission
NGI	Next Generation Impactor
NIR	Near Infra-Red
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance

NMT	Not More Than
NOAEL	No Observed Adverse Effect Level
OSA	Obstructive Sleep Apnoea
OVA	Ovalbumin
PAF	Platelet-Activating Factor
PAQLQ(S)	Paediatric Asthma Quality of Life Questionnaire
PDE	Permitted Daily Exposure
PE	Polyethylene
PEF	Peak Expiratory Flow
Ph Eur	European Pharmacopoeia
PIFR	Peak Inspiratory Flow Rate
PL	Package Leaflet
PP	Polypropylene
PPE	Protein Extravasation
PQRI	Product Quality Research Institute
PSD	Particle Size Distribution
PSUR	Periodic Safety Update Report
QL	Quantitation Limit
QOS	Quality Overall Summary
QPPV	Qualified Person Responsible for Pharmacovigilance
RH	Relative Humidity
RMP	Risk Management Plan
RRt	Relative Retention Time
Rt	Retention Time
RT	Room Temperature
SABA	Short-Acting B2-Agonist
SAL	Sterility Assurance Level
SEM	Scanning Electron Microscopy
SOC	System Organ Class
SPC. SmPC	Summary of Product Characteristics
Sx or SX	Salmeterol Xinafoate
t½	Elimination Half-Life
TGA	Thermo-Gravimetric Analysis
TGF	Transforming Growth Factor
TLC	Thin Layer Chromatography
tmax	Time to Maximum Observed Plasma Concentration
TV1	Treatment Visit 1
UDD	Uniformity of Delivered Dose
ULN	Upper Limit of Normal
UPLC	Ultra-Performance Liquid Chromatography

URI	Upper Respiratory Tract Infection
US	United States
WADA	World Anti-Doping Agency
WFI	Water for Injections
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva B.V. submitted on 14 October 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for BroPair Spiromax, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 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 applicant applied for the following indication:

"BroPair Spiromax is indicated for use in adults and adolescents 12 years and older.

BroPair Spiromax is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting β_2 agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 agonist."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

This application is submitted as a multiple of Seffalair Spiromax simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0245/2017 on the granting of a (product-specific) waiver.

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.

New active Substance status

The applicant indicated the active substances salmeterol xinafoate / fluticasone propionate contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 February 2018	EMEA/H/SA/3754/1/2018/II	*Armin Koch, Carin Bergquist*

The Scientific advice pertained to the following clinical aspects:

- *acceptability of the overall clinical development strategy, sufficiency of the generated safety data, acceptability of dosing regimen, sufficiency of safety data in the adolescent population, acceptability of comparator*

1.2. Steps taken for the assessment of the product

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

Rapporteur: John Joseph Borg Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	14 October 2019
The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 February 2020
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	14 February 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 October 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	8 October 2020

The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 January 2021
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 BroPair Spiromax on	28 January 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant has applied for the following indication: Regular treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta2-agonist (LABA) and inhaled corticosteroid (ICS) is appropriate: - patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonists, or - patients not adequately controlled with long-acting beta2-agonists and low dose of inhaled corticosteroids. This includes patients with mild to severe asthma not adequately controlled by the Global Initiative for Asthma (GINA) treatment step 2 or 3.

2.1.2. Epidemiology and risk factors

Asthma is a chronic inflammatory disorder of the airways associated with airways inflammation and hyper-responsiveness.

Asthma is a common disease affecting an estimated 340 million people worldwide. The prevalence of asthma is increasing in industrialised and developing countries and the number of persons with asthma is estimated to reach 400 million by the year 2025. The Global Asthma Report estimates that 23.7 million disability-adjusted life years are lost annually due to asthma, representing 1% of the total global burden. The prevalence in Europe is up to 10%.

It is estimated in Europe that 17% of patients have difficult to treat asthma and 3-4% have severe asthma (GINA).

2.1.3. Aetiology and pathogenesis

Asthma is a heterogenous disease with different underlying disease processes, different phenotypes (recognizable clusters of demographics, clinical and pathophysiological characteristics). The most recently identified phenotypes are allergic asthma, non-allergic asthma, late onset (adult onset) asthma, asthma with persistent airflow limitation and asthma with obesity.

The pathophysiology of asthma is characterised by inflammation and intermittent obstruction of the airways and bronchial hyper-responsiveness. Inflammation in asthma generally involves the same cells

involved in the allergic response in the nasal passages and skin, (atopy) and includes mast cells, eosinophils and Th2 lymphocytes.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Asthma is a heterogenous disease usually characterised by chronic inflammation. It is defined by the history of respiratory symptoms - wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation. These variations are often triggered by factors such as exercise, allergen or irritant exposure, changing weather or viral respiratory infections. Symptoms occur particularly at night or in the early morning. Symptoms (and airflow limitations) may resolve spontaneously or in response to medication and in cases may be absent for a period of time (weeks or months at a time). Patients may experience sudden exacerbations that may be life threatening, carrying a significant burden to the individual and the community. Asthma is usually associated with airway hyperresponsiveness to direct and indirect stimuli, and with chronic airway inflammation. These features persist even when symptoms are absent, or lung function is normal but may normalise with treatment.

Diagnosis is based on two key features:

- A history of variable respiratory symptom;
- variable expiratory airflow limitation and reversibility.

Patient scan be classified as mild, moderate and severe based on symptom control and treatment requirements.

2.1.5. Management

The long-term treatment goals are symptom control and risk reduction. Symptom control aims to have only occasional daytime symptoms without sleep disturbance or exercise limitation. Risk reduction involves preventing exacerbations, preserving lung function and avoiding asthma deaths.

The pharmacological options for long – term treatment of asthma fall into three categories:

- Controller medications [these are used to reduce airway inflammation, control symptoms, reduce future risk (exacerbations, decline in lung function] which should be initiated as soon as possible;
- Reliever (rescue) medications;
- Add- on therapies for patients with severe asthma.

Low dose ICS provides most of the clinical benefits for most of patients with asthma. However, ICS responsiveness varies between patients. Some patients will require medium dose ICS if their asthma remains uncontrolled, despite good adherence and inhaler usage technique.

In clinical practice, the choice of medication, device and dose should be based for each individual patient on assessment of symptom control, risk factor, patients' preferences and practical issues (e.g. cost, ability to use the device, and adherence).

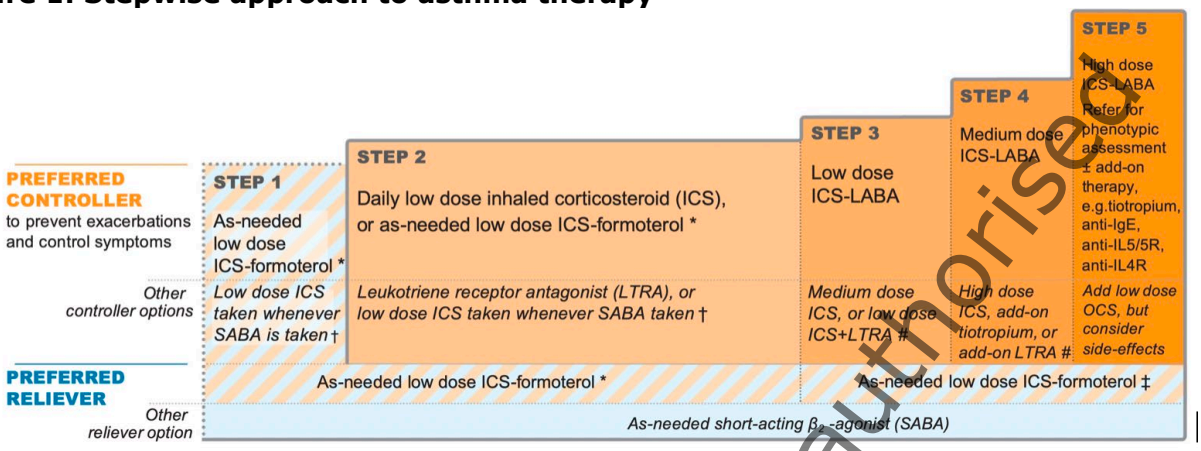
The stepwise approach to asthma treatment is widely use (Figure 1).

Patients not adequately controlled with a maintenance low dose ICS and 'as needed' short-acting beta2-agonists or LABA (GINA step 2 and 3) have the following treatment options in addition to optimising treatment compliance and modifying risk factors;

- Combination low dose LABA/ICS with as needed short acting beta2-agonists;

- Combination low dose formoterol/ICS maintenance and reliever.

Figure 1: Stepwise approach to asthma therapy



Recommended clinical practice in the treatment of asthma is to start at the lowest dose of medication and escalate to the mid- and high doses, as needed. After asthma control is achieved, recommendations are to step back to the lowest dose available, which can maintain symptom stability.

The step down should be considered when asthma symptoms have been well controlled and lung function has been stable for 3 or more months. If the patient has risk factors for exacerbations the past year or persistent airflow limitation, the step down should be closely supervised.

About the product

BroPair Spiromax multi-dose powder inhaler (also referred as 'FS MDPI') is an inhalation-driven multi-dose dry powder device containing a blend of fluticasone propionate (Fp), an ICS and salmeterol xinafoate (Sx), a LABA as actives substances.

Fp given by oral inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

Sx is a selective LABA with a long side chain which binds to the exosite of the receptor. Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short acting β_2 agonists. Salmeterol provides symptomatic relief, by reducing the bronchoconstriction.

The applicant initially seek approval for FS MDPI, at nominal doses of 50/12.5 (low), 100/12.5 (mid), and 200/12.5 (high) mcg bid, for the maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older.

Claimed Indications and recommendation for use

BroPair Spiromax is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting β2 agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2 agonist, or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist.

Proposed posology:

One inhalation of 14 micrograms salmeterol and 55 micrograms fluticasone propionate or one inhalation of 14 micrograms salmeterol and 113 micrograms fluticasone propionate or one inhalation of 14 micrograms salmeterol and 232 micrograms fluticasone propionate twice daily.

The same posology is proposed for adults and adolescents 12 years and older.

Once control of asthma is achieved, treatment should be reviewed, and consideration given as to whether patients should be stepped down to BroPair Spiromax containing a lower dose of the inhaled corticosteroid and then ultimately to an inhaled corticosteroid alone.

Type of Application and aspects on development

The Applicant has developed BroPair Spiromax to allow treatment of the entire spectrum of asthma patients for whom combination therapy is appropriate. The FS MDPI contains the same active ingredients (in lower amounts) as Seretide Accuhaler, which is marketed throughout Europe, and Advair Diskus, which is marketed throughout the US. The FS MDPI is marketed in both the US and Canada, with low-, mid-, and high-dose.

The Applicant considered that Advair Diskus and the EU equivalent product (Seretide Accuhaler) can be considered clinically the same based on their comparability. The comparability is also supported by their performance profiles *in vitro*. The in vitro profile of an Advair Diskus batch used in the clinical study (FSS-AS-305) fell within the profile for marketed batches of Seretide Accuhaler, indicating that Advair Diskus was a good representative for Seretide Accuhaler and specific clinical trials with Seretide Accuhaler were therefore not considered necessary by the applicant.

The FS MDPI delivers drug to the airways as a fine powder without the use of propellants. As an inhalation-driven device, FS MDPI eliminates the need for coordination of actuation and inspiration. The active ingredients are dispersed in a lactose monohydrate excipient and contained within a reservoir. A metered dose of drug is delivered to a dose cup via an air pulse-activated mechanism when the cap is opened.

The Applicant has developed a formulation containing drug and carrier particles of appropriate particle sizes that take advantage of the cyclone de-agglomerator; allowing for formulation drug concentrations in the FS MDPI to be significantly lower than those in Advair Diskus or Seretide Accuhaler, while achieving similar (or lower) systemic exposure and comparable clinical benefits. This novel, inhalation-driven MDPI device, does not require patient coordination of device actuation with inhalation, and has been used in the current programme with the goal of reducing administration errors associated with conventional metered dose inhalers (MDIs).

Despite the availability of combination products containing Fp and salmeterol for a number of years, the applicant considered that reducing the systemic exposure of salmeterol could potentially reduce the side effects due to this LABA while maintaining comparable efficacy, and thus developed BroPair Spiromax in a novel device at lower doses to offer an alternative option for some patients who are unable to tolerate the currently available products.

Regulatory History and Discussions with Health Authorities

The Applicant received National Scientific Advices from the Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom) and from the Medicinal Products Agency (MPA, Sweden), which covered the following topics related to clinical development:

- Both agencies agreed that the US-sourced comparators can be considered comparable, and they can provide relative efficacy and safety information for the EU application. Both agencies agreed that the programme conducted could be suitable. The MHRA commented it would be

important to demonstrate clearly that the lower doses administered with the Teva products (compared with the doses administered in the same fixed-dose combinations already available on the market) do not lessen the effect with respect to efficacy. The MPA commented that uncertainty with regard to dose potency relative to existing products on the market was of concern, so it would be valuable to at least have available *in vitro* data comparing the different strengths.

- Acceptability of the 6-month duration of Study FSS-AS-305 in adolescents and adults aged 12 years of age and older with asthma to assess long-term safety: Both agencies considered the duration could be adequate.
- Adequacy of the sample size of patients aged 12-17 years studied in the clinical programme to support use in adolescents in the EU (13-17 years): MPA commented that the data provided for adolescents would not be sufficient for a stand-alone assessment, but extrapolation of adult data would be accepted unless there were any specific concerns identified. MHRA commented that the number of adolescent patients is lower than would be considered ideal but could be adequate depending on the results.
- Acceptability of extrapolation of data from paediatric patients to the adolescent population, if necessary: MHRA agreed that extrapolation from data generated in children 12 years of age and younger to the adolescent population could be possible.

The Applicant did not mention the Scientific Advice received by CHMP (EMEA/H/SA/3754/1/2018/II, 22 February 2018), which raised some issues with respect to a part of the proposed indications and the need for evidence about which dose levels for approved products, the doses proposed with FS MDPI correspond to (please see sections 1.1 Submission of the dossier and 2.5.3 Discussion on Clinical Efficacy of this report).

2.2. Quality aspects

2.2.1. Introduction

The finished product BroPair Spiromax, also referred to as FS MDPI or as drug product, is presented as inhalation powder containing salmeterol xinafoate 12.75 micrograms in combination with fluticasone propionate in two different strengths: 100 or 202 micrograms.

The only other ingredient is lactose monohydrate.

Each delivered dose (the dose from the mouthpiece) contains 12.75 micrograms of salmeterol (as salmeterol xinafoate) and 100 or 202 micrograms of fluticasone propionate.

Each metered dose contains 14 micrograms of salmeterol (as salmeterol xinafoate) and 113, or 232 micrograms of fluticasone propionate.

The product is available in a white inhaler with a semi-transparent yellow mouthpiece cover. The parts of the inhaler coming into contact with the inhalation powder or the patient mucosa are made of acrylonitrile butadiene styrene (ABS), polyethylene (PE), and polypropylene (PP). Each inhaler contains 60 doses and is foil-wrapped with desiccant, as described in section 6.5 of the SmPC.

2.2.2. Active substance fluticasone propionate

General information

The chemical names of fluticasone propionate are androsta-1, 4-diene-17-carbothioic acid,6,9-difluoro-1-hydroxy-16-methyl-3-oxo-17-(1- oxopropoxy)- (6α,11β,16α,17α)-S-(fluoromethyl) ester, S-Fluoromethyl 6α, 9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate,17-propionate, (6α, 11β, 16α, 17α)- 6,9-difluoro-11-hydroxy-16- methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4- diene-17-carbothioic-acid,S-(fluoromethyl) ester and 6α, 9-difluoro-17-{(fluoromethyl)sulphanyl}carbonyl}-11β-hydroxy-16α-methyl-3- oxoandrosta-1,4-dien-17α-yl propanoate corresponding to the molecular formula $C_{25}H_{31}F_3O_5S$. It has a relative molecular mass of 500.6 g/mol and the following structure in Figure 2:

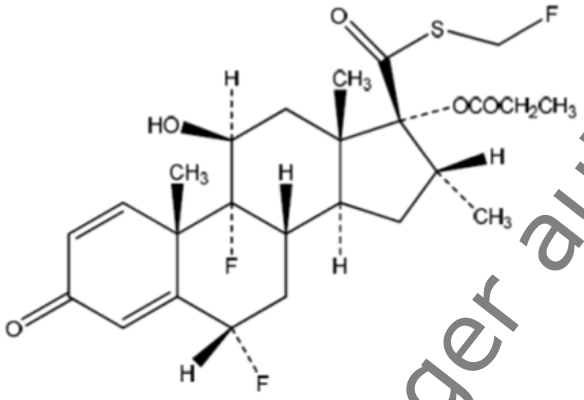


Figure 2: fluticasone propionate structure

The active substance is a white or almost white powder, non-hygroscopic and practically insoluble in water. It has multiple chiral centres but one single enantiomer, as shown in Figure 2 is obtained from the synthetic route and controlled in the specification via optical rotation.

During the procedure, in response to a major objection (MO), fluticasone propionate polymorphism has been discussed. Fluticasone propionate exhibits polymorphism with two known forms; Form I and Form II. The therapeutically relevant form is routinely produced by the CEP holder. The other form has only been obtained under supercritical fluid extraction techniques. The polymorphic forms of fluticasone propionate have been investigated by X-ray diffractometry (XRD), differential scanning calorimetry (DSC) and infrared (IR) tests, confirming that only desired form is present in the active substance. In response to the same MO, it has been demonstrated that morphology, crystallinity, specific surface area and morphic form are consistent also during the stability studies performed on the micronised active substance. Routine monitoring of morphic form is not required.

As there is a monograph of fluticasone propionate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for fluticasone propionate which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. Only one site is involved in the manufacture and micronisation of the active substance. Information on the micronisation process and validation was provided during the procedure in response to a major objection (MO). In response to the same MO, it was demonstrated that the controls employed for the validated crystallisation and micronisation procedures ensure consistent quality of the micronised active substance, as controlled in the active substance specification, which consequently results in consistent finished product performance.

The active substance is packaged in double polyethylene bags placed in a fibre drum. After micronisation, the active substance is stored in double polyethylene bags placed inside an aluminium foil liner. The polyethylene bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification, includes tests for: appearance (visual), identity (IR), specific optical rotation (Ph. Eur.), related substances (HPLC), residual solvents (GC), water content (Ph. Eur.), assay (HPLC), microbiological examination of non-sterile products (Ph. Eur.) and particle size distribution (laser diffraction).

The specification tests include all the monograph tests with the addition particle size distribution and residual solvents and microbiological examination, which is required for active substances used for inhalation route. The test for acetone described in the monograph is replaced by test for residual solvents by gas chromatography. The specification of the finished product manufacturer is fully in line with the specification of the active substance manufacturer. The finished product manufacturer has adopted the analytical methods for particle size distribution and residual solvents used by the CEP holder. All other analytical methods are as per Ph. Eur. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from five production scale batches were provided, demonstrating compliance with the proposed specifications. The batch data provided are considered to be sufficient. Consistency and uniformity of the active substance quality have been demonstrated.

Stability

As no re-test period is proposed in the CEP, stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the container stated in the CEP for up to 60 months under long term conditions (25°C ± 2°C, 60% ± 5% RH) and for up to 6 months under accelerated conditions (40°C ± 2°C, 75% ± 5% RH) according to the ICH guidelines were provided. The tested parameters were within the specifications. Additional data form three commercial scale batches of the micronised active substance stored in the proposed container used after micronisation for up to 48 months under long term conditions (25°C ± 2°C, 60% ± 5% RH) were provided. These batches were tested for particle size distribution only. The tested parameter was within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the retest period of 60 months when stored in the packaging stated in the CEP as proposed by the active substance manufacturer and of 24 months proposed by the finished product manufacturer.

2.2.3. Active substance salmeterol xinafoate

General information

The chemical name of salmeterol xinafoate are 4-hydroxy-α'-[[[6-(4-phenylbutoxy)hexyl]amino] methyl]-1,3-benzene dimethanol 1-hydroxy-2- napthoate; 4-hydroxy-α'-[[[6-(4-phenylbutoxy)hexyl] amino] methyl]-1,3-benzene dimethanol 1-hydroxy-2- napthelene carboxylate and (1RS)-1-[4-hydroxy-3-(hydroxy methyl)phenyl]-2-[[6-(4-phenyl butoxy)hexyl]amino]ethanol 1-

hydroxynapthalene -2-carboxylate corresponding to the molecular formula $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It has a relative molecular mass of 603.74 g/mol and the following structure in Figure 3:

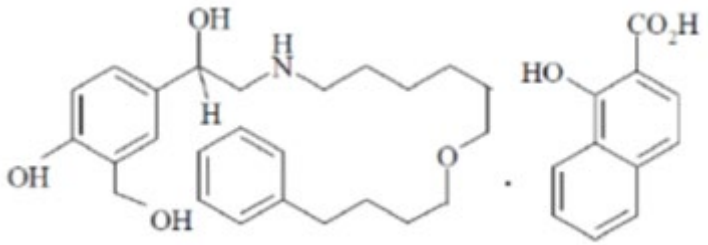


Figure 3: salmeterol xinafoate structure

The active substance is a white or almost white powder and is sparingly soluble in water. As stated in literature, salmeterol xinafoate is the racemic form of 1-hydroxy-2-naphtoic acid salt of salmeterol.

During the procedure, in response to a MO, salmeterol xinafoate polymorphism has been discussed.

Salmeterol xinafoate exhibits polymorphism with two known forms; Form I and Form II. The therapeutically relevant form is routinely produced by the CEP holder. The other form has only been obtained under supercritical fluid extraction techniques. The polymorphic forms of salmeterol xinafoate have been investigated by X-ray diffractometry (XRD), differential scanning calorimetry (DSC) and infrared (IR) tests, confirming that only desired form is present in the active substance. In response to the same MO, it has been demonstrated that morphology, crystallinity, specific surface area and morphic form are consistent also during the stability studies performed on the micronised active substance. Routine monitoring of morphic form is not required. As there is a monograph of salmeterol xinafoate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for salmeterol xinafoate which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Only one site is involved in the manufacture and micronisation of the active substance. Information on the micronisation process and validation was provided during the procedure in response to a MO. In response to the same MO, it was demonstrated that the demonstrating that the controls employed for the validated crystallisation and micronisation procedures ensure consistent quality of micronised active substance, controlled in the active substance specification, which consequently results in consistent finished product performance.
The micronised active substance is packaged in double polyethylene bags placed inside an aluminium foil pouch with a desiccant. The foil pouch is placed inside a high-density polyethylene container. The polyethylene bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance (visual), identity (IR), related substances (HPLC), residual solvents (GC), water content (Ph. Eur.), sulphated ash (Ph. Eur.), assay (HPLC), microbiological examination of non sterile products (Ph. Eur.) and particle size distribution (laser diffraction).

The specification tests include all the monograph tests with the addition of residual solvents, particle size distribution and microbiological examination, which is required for active substances used for

inhalation route. Although the CEP includes the test for palladium, the applicant has adequately justified its omission from the specification during the procedure.

The finished product manufacturer has adopted the analytical methods for particle size distribution and residual solvents used by the CEP holder. All other analytical methods are Ph. Eur. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from three production scale batches are provided, demonstrating compliance with the proposed specifications. Consistency and uniformity of the active substance quality have been demonstrated.

Stability

Stability data from three commercial scale batches of non-micronised active substance from the proposed manufacturer stored for up to 60 months under long term conditions (25°C ± 2°C, 60% ± 5% RH) and for up to 6 months at accelerated conditions (40°C ± 2°C, 75% ± 5% RH), and stability data from three commercial scale batches of micronised active substance for up to 60 months under long term conditions (25°C ± 2°C, 60% ± 5% RH) according to the ICH guidelines were provided.

These batches were tested for appearance, water, impurities and assay. Data on particle size was provided for 2 of the three batches stored at long term conditions for 24 months. The tested parameters were within the 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 by the active substance manufacturer of 60 months stored in the proposed packaging as stated in the CEP.

2.2.4. Finished medicinal product

Description of the product and Pharmaceutical development

Fluticasone propionate/salmeterol inhalation powder (FS MDPI) is a blend of fluticasone propionate and salmeterol xinafoate as the active pharmaceutical ingredients, and lactose monohydrate as a carrier.

An overage is introduced to account for the active substance loss during the finished product manufacturing process; adequate justification has been provided during the procedure. The target fill weight includes an overfill to ensure delivery of the label claim number of actuations (60).

The inhalation powder is a blend of the two active substances, fluticasone propionate (FP) and salmeterol xinafoate (SX) with lactose. Coarse lactose carries the micronised active substances particles on its surface up to the moment of inhalation, when the active substances de-aggregate and detach from the surface of the carrier. The fine lactose stearate modulates particle-particle interaction and therefore improves the de-aggregation/re-suspension of the active substances' particles in the inspired air flow during inhalation.

Lactose is a well-known pharmaceutical ingredient used for this route of administration and pharmaceutical form and its quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The aim of the pharmaceutical development was to develop lower strength alternatives to the already marketed long acting beta agonist (LABA) and inhaled corticosteroids (ICS) combinations achieving, the same efficacy as marketed inhalation powders using a lower strength of both active substances. Initially three strengths were developed (55/14 mcg, 113/14 mcg and 232/14 mcg); however only the two higher strengths are proposed for marketing. The lower strength has been used to generate some stability data which are of relevance for the two strengths proposed for marketing. Teva has already experience in the development of inhalation powders in the EU market using the same delivery device (e.g. DuoResp Spiromax EMEA/H/C/002348); in fact Aerivio Spiromax (EMEA/H/C/002752), which now is withdrawn, contained the same active substances as the proposed product at a higher strength and used the same delivery device.

Different batches of FP and SX with a range of particle size distribution (PSD) have been used in finished product development and evaluated for impact on blend uniformity (BU), dose content uniformity and aerodynamic particle size distribution (APSD). During development, lactose batches with a range of PSD focusing on the percentage of fine lactose (particulate below 10 micrograms) have been evaluated. Two optimised grades of lactose, Grade 4 and Grade 5 were selected for the manufacture of FS MDPI 232/14 and 113/14, respectively. The selection of the grades was based on the effect of fine lactose on the aerodynamic performance and the need to achieve proportionality between the various strengths of FS MDPI. The choice of the lactose grades has been fully justified.

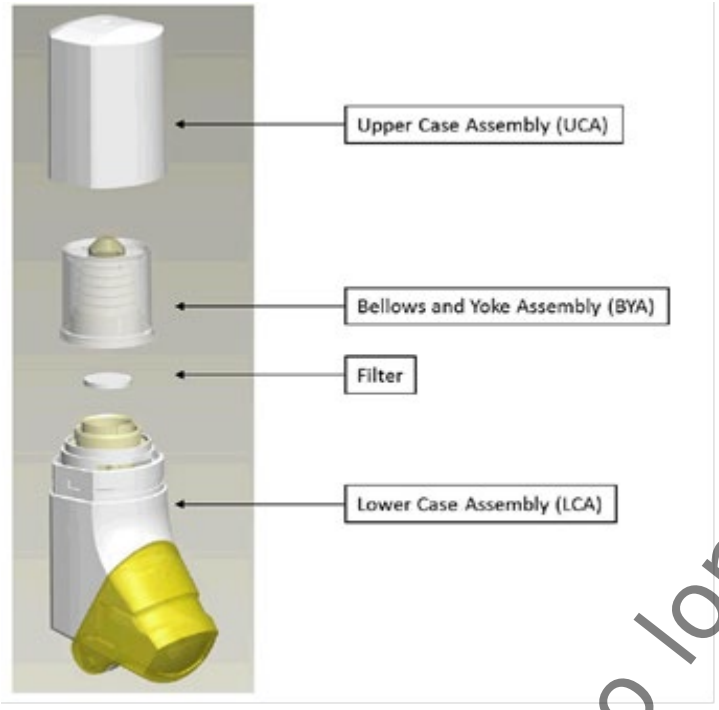
To address a MO, in addition to particle size, particle shape, rugosity and amorphous content of both active substances and excipient have been discussed in detail as these are critical material attributes that may influence the homogeneity, reproducibility and the performance and quality of the finished product for use via the inhalation route. It was concluded that PSD of the active substances and lactose is the only parameter that needs to be controlled as consistency of the other characteristics is ensured by the validated manufacturing methods of the components of the finished product.

The formulation and manufacturing development have been described in detail, from pilot scale to the commercial scale. The development programme was divided into two phases: development of a range of FS MDPI product strengths for a Phase 2b ranging clinical study to establish the appropriate doses for different asthma severities in placebo-controlled studies and development of a range of FS MDPI product strengths for Phase 3 efficacy and long-term safety clinical studies. The manufacturing process consists of blending the micronised active substances with the lactose, filling and equilibrating the devices, packaging and labelling of the devices. A design of experiments (DoE) was used to evaluate the main effects of the blending process parameters (i.e. impeller speed and mixing time) and material attributes on the blend uniformity and pharmaceutical performance. Product development and optimisation was continued with FS MDPI 50/12.5, 100/12.5 and 200/12.5 products. The formulation strategy was finalised for the Phase 3 clinical and registration programs such that all strengths were developed using the same delivery device, with each strength requiring its own blend. Comparison data between the FS MPDI and the products used in used in phase 3 clinical trials have been provided confirming that the product performance is equivalent.

The delivery device is a breath actuated multidose reservoir dry powder inhaler, hence the finished product and the device are considered to constitute an integral "drug device combination product". The inhaler is a white with a translucent yellow mouthpiece cover. Each inhaler consists of the following main components: upper case assembly, bellows and yoke assembly, filter, and lower case assembly as depicted in Figure 4 below. The parts of the inhaler coming into contact with the inhalation powder or the patient mucosa are made of acrylonitrile butadiene styrene (ABS), polyethylene (PE), and polypropylene (PP). The contact material complies 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. The same device is used for all strengths. Each inhaler contains 60 doses and is wrapped in a 4-ply foil laminate with desiccant to protect the products from moisture over long-term storage. The

same variant (NB7/3) of the device and the same secondary packaging have been used throughout the development of the product; the cup size used to measure the dose was optimised and fixed at the beginning of the development.

Figure 4: FS MDPI device components



The finished product characterisation studies were conducted in accordance with EMA guideline "Guidance on the Pharmaceutical Quality of Inhalation and Nasal products" (CHMP/QWP/49313/2005 Corr, June 2006). To assess the pharmaceutical performance of the FS MDPI product strengths, a bracketing approach for the middle strength was proposed. However, since the composition of the three strengths is not dose proportional and the blends are different, a MO on the acceptability of the bracketing approach used during pharmaceutical development, was raised requesting the missing *in vitro* data on the middle strength. This part of the MO was resolved by performing a flow rate study. It was demonstrated that the evaluated patient flow rates have no notable impact on the pharmaceutical performance of the product; it was concluded that the bracketing approach was acceptable. The finished product characterisation studies to determine that appropriate storage conditions, facilitate correct use and maintenance of the inhaler, and contribute to patient compliance were originally conducted applying the delivered dose testing regime described by the US FDA Draft Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (1998) (one delivered dose is measured at the beginning, middle and end of inhaler life and is referred to as Dose Content Uniformity through life (DCU-TL)). To validate the data generated using this approach, a comprehensive study bridging the adopted testing regime to the one described by Ph. Eur. (3 beginning, 4 middle and 3 end of inhaler life) in the uniformity of delivered dose (UDD) as required described in the Ph. Eur. has been conducted. Based on this study it was concluded that the differences in the test regime do not impact on data generated, as the DCU results are statistically comparable to the UDD results.

Manufacture of the product and process controls

The manufacturing process consists of 4 main stages: blending, filling, device assembly, packaging. The process is typical for manufacturing of inhalation powders, which are normally considered

specialised pharmaceutical forms and their manufacture is considered to be a non-standard process. Controls are applied to critical steps of the manufacturing process.

The manufacturing process as well as in-process controls performed have been sufficiently described. In-process controls have been identified and are considered adequate.

The holding times of each step, including the equilibration step, have been adequately justified.

Major steps of the manufacturing process have been validated during process validation at commercial scale on three batches per strength for each site. 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 this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance and description of the inhaler, dose counter and of the powder (visual inspection), identification (UPLC and TLC), assay (content per inhaler UPLC), related substances (UPLC), water content (Karl Fischer), net content (fill weight), uniformity of delivered dose (Ph. Eur.), number of actuations per inhaler, dose counter reading (at actuation 58), APSD (next generation impactor (NGI) Ph. Eur.), microbiological examination for non-sterile products (Ph. Eur.).

The proposed finished product specification contains the required tests for this dosage form and it is in line with the "Guidance on the Pharmaceutical Quality of Inhalation and Nasal products" (CHMP/QWP/49313/2005 Corr, June 2006) and the "Preparations for Inhalation" Ph. Eur. monograph.

The limits for impurities and degradation products at release and during shelf-life are in agreement with ICH Q3B. The limit for assay has been tightened to 90-105 % during the procedure in line with batch and stability data. The applicant is recommended to monitor the first 20 commercial batches of the finished product for assay and eventually to tighten the specifications limits further (see Recommendation).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches of the highest dose, which represent the worst-case scenario, using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, in response to a MO, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for twelve commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

The applicant proposes a shelf-life of 18 months and of 2 months after opening the foil with certain precautions for storage.

Stability data from 9 commercial scale batches of development strength (low, middle and high) of the finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (40 ºC / 60% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary and secondary (protective film foil with desiccant) packaging proposed for marketing. The inhalers were stored in the upright and inverted position.

The in-use stability studies were conducted over a period of 3 months on the low and high strength (bracketing approach) of the batches used for the long term stability study, to assess the product performance, after being dispensed to the patients outside the protective film foil and kept under intermediate conditions (30 ºC / 60% RH) for up to two months. The inhalers were stored in the horizontal position.

Samples were tested in line with the shelf-life specification given. The analytical procedures used are stability indicating.

No significant changes were observed in the long term, accelerated studies and in-use studies and all results were within the proposed specification limits.

Of note the impact of moisture was also investigated during development studies on the un-pouched inhalers under low, medium and high humidity (25°C/less than 30% RH, 25°C/60% RH and 25°C/75% RH, respectively) on three batches of the low and high strength (bracketing approach). The effect of moisture was assessed by testing inhalers for DCU, DCU-TL, APSD and water content. The results of the study demonstrate that different levels of moisture exposure have no impact on the pharmaceutical performance of both product strengths.

No photostability stability studies were performed due to the nature of the container closure system. Since the DPI excludes light, this is accepted.

The applicant had initially proposed different shelf-lives for different strengths, but this was not accepted. Based on available stability data, the proposed shelf-life of 18 months and of 2 months after opening the foil with the following precautions for storage: 'Do not store above 25°C. Keep the mouthpiece cover closed after use' as stated in the SmPC (section 6.3) are accepted.

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.

2.2.5. 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.

In response to three major objections raised one for each active substance and one of the finished product development on the characterisation of the finished product components, the applicant has supplemented the submission with additional information on the physico-chemical characteristics of the active substance which could have an impact on the aerodynamic performance of the product. In response to the same MO raised for the finished product the bracketing approach used during the development has been adequately justified. The risk of nitrosamine contamination was also evaluated to address a MO and no risk was identified. 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.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, resulting in the recommendation to monitor the first 20 commercial batches of the finished product for assay and eventually to tighten the specifications limits further was agreed.

2.2.6. 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.

2.2.7. Recommendation for future quality development

3.2.P.5 - The applicant is recommended to monitor the first 20 commercial batches of the finished product for assay and eventually to tighten the specifications limits further, if supported by data.

2.3. Non-clinical aspects

2.3.1. Introduction

Fluticasone propionate (Fp) and salmeterol xinafoate (Sx) have been used via inhalation alone and together for treatment of upper respiratory diseases for several years. The pharmacological and toxicological aspects of the respective individual and combined products have been well characterised and extensively reviewed.

Fluticasone propionate is a potent fluorinated glucocorticoid with anti-inflammatory activity that is commonly used to treat asthma and allergic rhinitis. It has been marketed in the EU for many years and has been shown to reduce symptoms and exacerbations of asthma and to decrease airway reactivity to histamine and methacholine in patients with hyperreactive airways. It is a well-established active substance and is recommended for use in the management of asthma in both adults and adolescents.

Salmeterol xinafoate is a long-acting β-agonist bronchodilator that exerts a preferential effect on β2-adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilation that lasts

for 12 hours after a single dose. It is used via the orally inhaled route in the management of patients with reversible airways obstruction associated with mild to moderate asthma and 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.

The fluticasone propionate/salmeterol (FS) combination is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting β2-agonist) is appropriate: in patients no adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β2-agonist or in patients already adequately controlled on both inhaled corticosteroid and long-acting β2-agonist. FS fixed-dose combination products have been marketed in the EU for over 20 years in dry powder inhalation formulation.

Taking into account available information from published pharmaco-toxicological literature on Fp and Sx and on their use in combination which sufficiently demonstrated the safety and the efficacy of those active substances, no new non-clinical studies were conducted by the applicant to directly support this application. The information presented in the below sections are based on literature data.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamics

Fluticasone propionate (Fp)

The anti-inflammatory activity of fluticasone propionate has been demonstrated by its effects on a number of inflammatory mediators and markers *in vitro* and *in vivo*.

In vitro studies

In vitro studies have shown that Fp potently inhibits anti-CD3-induced proliferation of T-cells taken from normal volunteers, with a median effective dose (ED50; at approximately 0.3 nM) that is lower than budesonide (0.8 to 2.0 nM) and dexamethasone (5.9 nM). Fp also more potently inhibits phytohaemaglutinin-stimulated proliferation of lymphocytes compared to budesonide and beclomethasone dipropionate. The proliferation of lymphocytes from corticosteroid-resistant patients could also be inhibited by Fp.

Cytokine generation is inhibited by Fp in a range of human cells. In mast cell studies, Fp was found to have median inhibitory concentration (IC50) values of <1 nM for inhibition of interleukin (IL)-4, IL-6, IL 8 and tumour necrosis factor (TNF)-α. Concentrations required to inhibit epithelial cell cytokine production were slightly greater, with IC50 values of 5, 10, and 1 nM for inhibition of IL-6, IL-8, and granulocyte-macrophage colony stimulating factor, respectively. However, Fp potently inhibited epithelial TNF-α generation, with an IC50 value of 0.1 nM. Fp has also been shown to inhibit platelet-derived growth factor stimulated production of IL-l-β and IL-6 in human alveolar macrophage and fibroblast cells. The IC50 value was found to be 0.1 nM for inhibition of IL-l-β and IL-6, respectively, in both cell types.

In vivo studies

Guinea pigs treated with Fp before intratracheal IL-5 administration showed potent Fp-related inhibitory activity against IL-5-induced eosinophilia when eosinophil numbers in bronchioalveolar lavage fluid (BALF) were measured after 24 hours.

Inhibition of histamine challenge-induced mucosal oedema, a model not traditionally recognised as being highly corticosteroid responsive, has also been investigated. There was some inhibition with

beclomethasone dipropionate (BDP) at the earliest time, but this was rapidly lost. In contrast, Fp, at 10% of the dose of BDP, gave a marked and longer lasting response.

A 5% toluene disocyanate solution was administered intranasally to rats, over an 8-week period, to increase mast cell proliferation in nasal mucosa. Fp treatment was found to potently inhibit this response; an intranasal dose of 50 mcg/day reducing mast cell numbers to basal levels. The study demonstrates the ability of Fp to decrease inflammatory cell accumulation induced by an intranasal stimulus. Studies in rodents were conducted to quantify and compare anti-inflammatory activity after topical administration of Fp and the ability to produce specific systemic steroid-related effects after topical, oral, or parenteral administration. Topical anti-inflammatory activity was measured in rats and mice using the inflammatory response to croton oil applied topically to the ear. Results showed that Fp was essentially equipotent with fluocinolone acetonide in both rats and mice. Systemic responses to repeated topical applications of Fp were assessed by measurement of thymus involution and reduction in stress-induced plasma corticosterone (hypothalamic-pituitary-adrenal [HPA] axis suppression) in rats and mice, and adrenal atrophy in the rat. In these tests Fp was 50-100 fold less potent than fluocinolone acetonide in the rat (56-fold greater therapeutic index) and 100-times less potent than fluocinolone acetonide in mice (relative therapeutic index 91). Therefore, in both species, the separation between topical anti-inflammatory and systemic activity after topical application was highly favourable to Fp. Comparison of systemic activity after topical and subcutaneous dosing of Fp shows that, in both rats and particularly in mice, Fp is more potent when given subcutaneously. After oral dosing in rats, Fp caused some thymus involution, adrenal atrophy and HPA axis suppression but was 6- to 38-times less potent than betamethasone alcohol. In the mouse, oral Fp is 60- to 200-times less potent than betamethasone alcohol.

Animal studies of the relative anti-inflammatory and HPA axis inhibitory potencies of topically applied drug demonstrated that Fp has an advantageous therapeutic index (>200-times that of beclomethasone dipropionate).

In an ovalbumin (OVA) challenge assay in mice, intranasal administration of fp can modulate the remodelling of airway smooth muscle via regulation of transforming growth factor (TGF)-β1 production and active TGF-β1 signalling. When rats were exposed to aerosolised OVA (1%), the allergen-induced progression of established structural airway changes could be inhibited by treatment with inhaled Fp.

In monkeys, Fp markedly inhibited allergen (dinitrophenol Ascaris suum allergen [DNP A])-induced airway hyperresponsiveness (AHR) in an asthma model. Similar effect was observed after the treatment with prednisolone.

Salmeterol Xinafoate (Sx)

In vitro studies

The persistent action of the drug could be fully reversed by the β1- and β2-adrenoceptor blocker, sotalol, but when the antagonist was washed out, the activity of Sx was reasserted. Despite the sustained agonist action, no tolerance or tachyphylaxis has been observed with Sx in respiratory smooth muscle. Binding studies suggest that the long duration of effect of salmeterol is due to a unique method of action whereby a portion of the molecule binds with high affinity to nonpolar domains or exosites from where the rest of the molecule can interact freely with the active site of the β2 adrenoceptor.

The pharmacologic effects of β2-adrenoceptor agonist drugs, including Sx, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibit the release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Sx also inhibits the release of pro-inflammatory and spasmogenic mediators in the lung by an action at β2-adrenoceptors on mast cells. Histamine, leukotriene, and prostaglandin D release from human lung fragments *in vitro* is inhibited by Sx in a concentration dependent manner.

There has been some debate about the anti-inflammatory properties of Sx. *In vitro* it has a potent effect on the IgE-dependent release of histamine, prostaglandin D2, and leukotrienes C4 and D4 from passively sensitised human lung fragments, achieving log IC50 values of 8.54, 9.07, and 8.8, respectively. As with its effect on smooth muscle, the response has a long duration (>20 hours) and is competitively antagonised by propranolol. Because mast cells are the predominant source of mediators with reversed anaphylactic challenge, this inhibitory effect of Sx enhances its therapeutic potential in asthma.

Sx, and the related substance salbutamol, do not inhibit IL-1 β production *in vitro*, but both inhibit TNF-α secretion by lipopolysaccharide-activated TPH-1 cells with an IC50 of approximately 0.1 mcM. This inhibition is reversible by β2-antagonists. In T-cells, salmeterol inhibits activation (proliferation and IL-2 secretion in response to anti-CD3 antibody) at about 1 mcM but this effect is not reversible by β2-antagonists.

Sx inhibits the formation of thromboxane through inhibition of leukotriene-B4 but these effects are only seen at high concentrations and are not susceptible to blockade by propranolol, suggesting that this response is a non-specific effect on the cell membrane.

Several *in vitro* studies suggest that Sx may significantly influence mucociliary clearance by increasing ciliary beat frequency and attenuating the ciliary beat frequency slowing induced by Pseudomonas aeruginosa toxin pyocyanin. Sx also demonstrated anti-inflammatory effects by inhibition of the release of inflammatory mediators including histamine, thromboxane, and leukotriene.

In vivo studies

In the isolated guinea pig fundus preparation, Sx produced smooth muscle relaxation. The concentration required to cause relaxation of guinea pig fundus, containing β3-adrenoceptors, was at least 1000-fold of that required to activate β2-adrenoceptors in airways smooth muscle, confirming the selectivity of Sx.

The potency and duration of action of the bronchodilator activity of Sx was determined in conscious guinea pigs following inhaled and oral administration. Nebulised aerosols of 0.012-12 mcM (equivalent to 5-5000 mcg/mL) caused dose-related inhibition of histamine-induced bronchoconstriction, with bronchodilator activity being similar to Sx. There were no clear differences between the durations of action of Sx and salbutamol by the oral route. However, following inhaled administration, the duration of action of Sx was substantially longer, exceeding 6 hours, compared with 1.5-3 hours for salbutamol.

In conscious guinea pig, inhaled Sx and salbutamol were approximately similar in producing dose-related inhibition of histamine-induced bronchoconstriction over a concentration range of 0.012-12 mM. However, at threshold effective concentrations, the duration of protection afforded by Sx exceeded 6 hours compared to <1.5 hours with salbutamol.

Sx has been shown to inhibit the extravasation of protein into the airways of guinea pigs challenged with histamine aerosol in a dose-dependent manner with duration of 6-8 hours. Because this protection was blocked by prior treatment with propranolol, it involved stimulation of β2-adrenoceptors. Activation of these receptors has been reported to maintain the integrity of the endothelial cell gap junctions, thereby preventing leakage of plasma proteins into the extravascular compartments.

Sx has also been shown to inhibit acute leukocyte influx after endotoxin (neutrophils), platelet-activating factor (PAF), and antigen (eosinophils) challenge of guinea pig airways *in vivo*, whereas in these models salbutamol is ineffective. A possible explanation for these findings may be found in

considering the time course of cell infiltration in these models, which ranges from 4 to >8 hours. Over this period, any inhibitory effects of short-acting β-agonists (such as salbutamol) will decline, whereas this will not be the case with salmeterol.

All β2-agonists relax the tissue of isolated airways (eg, guinea pig trachea) when tone is induced with prostaglandin PGF2α, carbachol, or through electrical stimulation. However, whereas the onset of action of isoprenaline, salbutamol, and fenoterol is rapid (<4 minutes), Sx is slow to reach equilibrium under these conditions.

Nebulised aerosols of Sx (0.001-1 mg/mL) caused a dose-related inhibition of plasma protein extravasation (PPE) induced by histamine. Both Sx and salbutamol had an ED50 of approximately 0.01 mg/mL, but the duration of action of Sx was substantially longer, being 6-8 hours compared with less than 2 hours for salbutamol. Orally administered Sx (0.01-1 mg/kg) also reduced histamine-induced PPE in a dose-related manner with an ED50 of 0.02 mg/kg. Prior treatment of animals with propranolol abolished the inhibition of PPE, indicating that these effects were mediated by β-adrenoceptors, probably at the level of the vascular endothelium.

The effects of Sx on behavior, muscle tone, reflexes, and autonomic function were investigated after intravenous dosing in the dog and acute oral administration in the conscious rat and dog. These effects were consistent with the known pharmacology of β2-adrenoceptor agonists.

Fluticasone and Salmeterol Combination (FS MDPI)

The combination can offer a more convenient regime for patients requiring concurrent LABA and ICS. The products are designed to produce a greater improvement in pulmonary function and symptom control than either fluticasone propionate or salmeterol used alone at their recommended dosages.

β2-agonists relax airway smooth muscle, but also inhibit mediator release from mast cells, prevent plasma exudation and inhibit activation of sensory nerves, whereas corticosteroid have inhibitory effects on the cells of chronic inflammation, including T-lymphocytes, eosinophils, macrophages, and dendritic cells, resulting in reduced airway hyper responsiveness. Corticosteroids increase the expression of β2-receptors and protect them against down-regulation in response to long-term β2-agonist exposure, whereas β2-agonists may enhance the anti-inflammatory actions of corticosteroids. Thus, each class of drug enhances the others beneficial actions.

Sx, in combination with Fp, can enhance glucocorticoid receptors (GR) nuclear translocation in vivo, as well as *in vitro*, and the data suggest that Sx may play an important role in the additional benefits seen with combination therapy. GR are specific cytoplasmic transcription factors that mediate the biological action of corticoids. *In vitro*, the enhanced GR nuclear translocation is associated with an amplified GR functional response. This may account, at least in part, for the effect seen with Sx alone *in vivo*.

Overall, the combination of Sx and Fp is considered to enhance aspects of allergen-induced airway remodelling without causing changes in airway responsiveness.

2.3.2.2. Secondary pharmacodynamics

Fluticasone propionate (Fp)

Fp has not been associated with adverse effects on the cardiovascular or central nervous systems.

Fp has been screened for a wide range of steroid hormonal or anti-hormonal activity in rats and mice and was found to be devoid of androgenic, anabolic, estrogenic, and anti-gonadotrophic activity, while some progestational, anti-androgenic, and anti-estrogenic activity was noted in oestrogen-primed

weanling rabbits. Weak anti-anabolic activity, another characteristic of potent glucocorticoids, was observed in the castrated rat. Fp lacked mineralocorticoid activity but caused significant diuresis and urinary excretion of sodium and potassium. In dogs, Fp administered via inhalation at dose levels 3-fold higher than the maximum recommended clinical dose, has been associated with marked suppression of plasma cortisol concentrations and adrenal function.

Corticosteroids attenuate the immune and inflammatory response by several mechanisms. Local administration of corticosteroids is used extensively in the treatment of asthma and allergic rhinitis and is considered to be the most efficient safe anti-inflammatory treatment currently available. Several studies have shown that ICS decrease the number of eosinophils in the airways of asthmatic patients and reduce the presence of eosinophil granule proteins in BALF. The effect of ICS after repeated allergen exposure-induced bone marrow activation and airway eosinophilia was investigated by assessing the number of eosinophils in bone marrow, BALF, and airways tissue in a BALB/c mouse model. Treatment with Fp significantly reduced the increase of absolute number of mature bone marrow eosinophils and showed a tendency towards decrease in the immature bone marrow eosinophil number compared to controls. However, Fp had no significant effect on BALF and airways tissue eosinophils. In this murine allergy model, intranasal corticosteroid reduced number of bone marrow mature eosinophils, but did not significantly affect airways cell populations.

Salmeterol xinafoate (Sx)

Salmeterol-related effects on behaviour, muscle tone, reflexes, and autonomic function have been evaluated from a non-clinical viewpoint; the results were consistent with the known pharmacology of β2 adrenoceptor agonists. In addition, Sx has been associated with signs such as vasodilation, tachycardia, vomiting, and decreased activity, which were all attributed to exaggerated pharmacology. No evidence of dysrhythmia or significant changes in electrocardiogram data has been noted in monkeys.

Fluticasone and Salmeterol Combination (FS MDPI)

In anaesthetised guinea pigs, there was no marked effect on the cardiovascular system when Fp was administered prior to Sx. Fp administered subcutaneously for 14 days to mice did not affect the contraction of isolated uteri due to Sx, showing no drug interaction.

Doses of less than 25 mg/kg/day of Fp and Sx in rats are capable of eliciting significant skeletal muscle hypertrophy with minimal or no cardiac hypertrophy, thus highlighting their significant clinical potential for muscle wasting conditions.

2.3.2.3. Safety Pharmacology

No new safety pharmacology studies were conducted for this submission.

A safety pharmacology study outlined in an approved (Advair) product determined the potential interaction of subcutaneously administered Fp with the cardiovascular and respiratory effects of intravenously administered Sx in anaesthetised guinea pigs. Salmeterol at doses (including and exceeding those required for pharmacological effects or amounts likely to be absorbed clinically after inhalation), had no effects other than those consistent with the known pharmacological profile of the compound (decreases in blood pressure and increases in heart rate). These effects were not exacerbated by pre-treatment with Fp.

2.3.2.4. Pharmacodynamics drug interactions

No pharmacodynamic interaction animal studies were conducted with the combination.

Non-clinical interaction studies would not add to the body of data already available, based on the fact that there is sufficient clinical experience with combined use of the individual medicinal products in patients.

Preterm birth was induced with a combination of mifepristone and prostaglandin E2 on day 19 of pregnancy. Rats were treated with Sx or gestagens (progesterone or 17- hydroxyprogesterone) or their combination. The treatments were launched on different days (15-18) of pregnancy. The efficacy of treatment was determined in terms of the delivery time counted from the mifepristone injection. Salmeterol treatment delayed premature labour by 2.4 hours, whereas the delay due to gestagen-salmeterol combinations was more than 5 hours. Parallel treatment with salmeterol and gestagens can be more than twice as effective as Sx therapy alone.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histological evidence of myocardial necrosis) when β-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown. This is reflected in section 5.3 of the SmPC.

2.3.3. Pharmacokinetics

Absorption

Fluticasone propionate (Fp)

Fp is associated with low oral bioavailability due to poor absorption and extensive first-pass metabolism; however, the majority of Fp delivered to the lung is systemically absorbed.

Due to low oral bioavailability, the swallowed portion of inhaled dosages should have less systemic effect than other inhaled steroids. Evidence to support this hypothesis has been obtained by measuring plasma cortisol, as an index of adrenal suppression, during Fp administration. Orally administered Fp, in doses up to 16 mg, had no effect on plasma cortisol levels. Intranasal Fp 2 mg twice daily for 7 days also had no effect on plasma cortisol. Inhalation administration to rats involves a significant ingestion of the dose, with subsequent excretion via the feces. Direct pulmonary dosing in dogs involved higher systemic exposure.

Salmeterol xinafoate (Sx)

Salmeterol is extensively absorbed across the gastrointestinal tract in both rat and dog after oral administration. However, the clearance of Sx is about 3-times higher in rat than in dog, indicating that hepatic extraction is also higher in the rat.

In radiolabelled studies in rat, dog, mouse, and pregnant rabbit, peak plasma levels were attained within 1 hour of dosing and were much lower than the mean peak concentrations of total drug related material, indicating extensive metabolism. However, Sx represented a much higher proportion of the circulating radioactivity in the dog than in the rat. This is consistent with the oral bioavailability of Sx being lower in rats (<15%) than in dog (approximately 60%).

The maximum concentration of Sx detected in plasma from animals in repeat-dose, combined oral/inhalation toxicity studies exceeds by several hundred-fold the maximum concentrations (200 pg/mL) determined after the standard therapeutic dose in humans. Salmeterol acts locally in the lung; the applicant therefore considered that plasma levels do not predict therapeutic effect. Because of the low therapeutic dose, systemic levels of Sx are low or undetectable after inhalation of the recommended dose in humans.

Fluticasone and Salmeterol Combination

Both Fp and Sx work locally in the lung; therefore, plasma levels do not predict therapeutic effect in humans.

Toxicokinetic data from the Fp/Sx combination studies generally showed dose-related but not dose-proportional increases in plasma concentrations. In a single dose inhalation study in dogs, Fp and Sx were administered as a powder in a 1:1 combination and Sx was absorbed faster and to a greater degree than Fp.

Distribution

Fluticasone propionate (Fp)

Studies examining the distribution of radiolabeled Fp in rats have shown that only traces of radioactivity pass into the systemic circulation after an oral dose. When administered orally to pregnant rats (100 mcg/kg) or rabbits (300 mcg/kg), a very small fraction of the dose (<0.005%) passes across the placenta.

Fp binds to the same high degree (94.6-96.5%) to plasmas proteins of rats, dogs, and humans. Fp is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin. Fp binds to a lower degree (17-31%) to the red blood cells in rats, dogs, and humans.

Salmeterol xinafoate (Sx)

The distribution of Sx in body tissues is consistent with that expected of a highly lipophilic base. At least 93% of the Sx distributed between erythrocytes and plasma is reversibly bound to the plasma proteins, β1-acid glycoprotein and albumin, in the mouse, rat, rabbit, dog, and man. The high plasma clearance of Sx indicates that changes in the degree of protein binding are unlikely to influence the rate of elimination.

Fluticasone and Salmeterol Combination

A placental study in mice showed that both Fp administered subcutaneously at 100 mcg/kg and Sx administered orally at 10 mg/kg crossed the placenta. Based on radioactivity, Fp crosses the placenta to a greater degree than Sx. Their levels in the fetuses were low as the maximum percent of the dose was 0.2% for Fp and 0.043% for Sx.

Metabolism

Fluticasone propionate (Fp)

Around 64% of an inhaled or intranasal dose of Fp is swallowed and then excreted unabsorbed in the feces as the unchanged compound. The remainder of the dose is subject to rapid and extensive metabolism in the liver, either pre-systemically following absorption from the gastrointestinal tract or after absorption from the site of administration into the systemic circulation.

In mice, rats, and dogs, Fp partially undergoes hydrolysis of the –COSCH2F substitution at the 17-position to the –COOH derivative. In dogs, Fp also undergoes defluorination at the 6 position. Both metabolites are excreted as the glucuronide. The predominant route of excretion for the metabolites and unchanged Fp was fecal.

The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of Fp, which is formed through the CYP 3A4 pathway. This metabolite had less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Salmeterol xinafoate (Sx)

Salmeterol is extensively metabolised by the liver. An *in vitro* study using human liver microsomes showed that Sx is extensively metabolised to α-hydroxysalmeterol (aliphatic oxidation) by CYP 3A4. This metabolite strongly binds to guinea pig tracheal tissue. Ketoconazole, a strong inhibitor of CYP 3A4, essentially completely inhibited the formation of α-hydroxysalmeterol *in vitro*.

In humans, Sx undergoes aliphatic oxidation, whereas in rat, rabbit, and mouse the predominant metabolic route is glucuronidation of Sx. The major Sx metabolite in the dog was identified as the 3-catechol sulphate of the benzoic acid derivative. The major metabolite of Sx in humans, hydroxylated on the butyl chain, is only a minor metabolite in the rat. However, exposure to this metabolite during rat toxicology studies was 100-fold greater than in human. This metabolite, 1-hydroxy-2-naphthoic acid (HNA), is pharmacologically active, but the effect is of shorter duration than that of Sx.

Elimination

Fluticasone propionate (Fp)

Pharmacokinetic data from laboratory animals indicate a rapid and extensive metabolic clearance with rapid elimination in the bile and excretion in feces. This is supported by results from radiolabeled dosing via intravenous route to rats and dogs and via oral and subcutaneous routes in mice, rats, and dogs. Studies in bile-duct cannulated animals support biliary excretion. No unchanged drug is excreted in the bile of rats or dogs, but a significant amount (up to 40%) of unchanged compound was found in the feces of dogs dosed orally with fluticasone propionate. Renal excretion is of minor importance, as urinary excretion accounts for less than 5% of a parenteral dose.

Oral or subcutaneous Fp administration to lactating rats resulted in measurable levels in milk. It is not known if Fp is excreted into the milk of lactating humans.

Salmeterol xinafoate (Sx)

In all species, Sx and its metabolites are excreted predominantly in the bile. Enterohepatic circulation of Sx has been demonstrated in the rat; however, no enterohepatic circulation of drug-related material occurs in the dog.

With the exception of the rabbit, HNA accumulated on repeat dosing in animals. Accumulation was also observed in humans, but the steady-state concentrations in humans are 1000-fold lower than those seen in species used in toxicology testing. It is unlikely that the major metabolite of HNA in humans is the same as that in rat. HNA and its metabolites are excreted predominantly via urine.

Studies have shown that Sx and its metabolites are excreted into the milk of lactating animals.

Pharmacokinetic Drug Interactions

Nonclinical PK interaction studies would not add to the body of data already available because there is sufficient clinical experience with combined use of the individual medicinal products in patients.

Fluticasone propionate (Fp)

Fp is a substrate of CYP 3A4. The use of strong CYP 3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with Fp products is not recommended because increased systemic corticosteroid adverse effects may occur.

A drug interaction trial with Fp aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP 3A4 inhibitor) can significantly increase plasma Fp exposure, resulting in significantly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving Fp and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Clinical coadministration of orally inhaled Fp (1000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma Fp exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

Salmeterol xinafoate (Sx)

Salmeterol is also a substrate of CYP 3A4. The use of strong CYP 3A4 inhibitors (eg, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with salmeterol products is not recommended because increased cardiovascular adverse effects may occur.

In a drug interaction trial in 20 healthy human subjects, co-administration of inhaled Sx (50 mcg twice daily) and oral ketoconazole (400 mg once daily) for 7 days resulted in greater systemic exposure to Sx (AUC increased 16-fold and Cmax increased 1.4-fold). Three subjects were withdrawn due to β2-agonist side effects (2 with prolonged QTc and 1 with palpitations and sinus tachycardia). Although there was no statistical effect on the mean QTc, coadministration of Sx and ketoconazole was associated with more frequent increases in QTc duration compared with Sx and placebo administration.

Salmeterol products should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of Sx on the vascular system may be potentiated by these agents.

Salmeterol did not affect pentobarbitone-induced sleeping time in mice suggesting it is unlikely to interfere with hepatic drug metabolism.

Fluticasone and Salmeterol Combination

Plasma concentrations of Sx and Fp administered concomitantly were determined in single dose inhalation studies in the rat and dog. Plasma levels at the lowest dose levels used in the studies (28/73 mcg/kg in the rat, and 48/50 mcg/animal in the dog) were about 30-fold and 26-fold greater in rat and 13-fold and 3- to 5-fold greater in dog than the peak levels likely to occur in man for Sx and Fp.

Repeat dose pharmacokinetics of Sx and Fp has been obtained by monitoring plasma concentrations in inhalation toxicity studies in the rat and dog. In both species, plasma levels of Fp were not affected by concurrent salmeterol administered and plasma levels of salmeterol were not affected by co-administration with Fp.

2.3.4. Toxicology

The toxicological aspects of the respective individual and combined products have been very well-characterised and summarised in previous regulatory reviews, approved product labels, and published literature that are available in the public domain. The toxicological profile of Fp and Sx is generally characterised by the exaggerated glucocorticoid and β-agonist pharmacological activity of each drug. The applicant did not provide additional nonclinical studies as there is sufficient clinical experience with the individual and combined products in patients.

2.3.4.1. Single dose toxicity

Fluticasone propionate (Fp)

In acute toxicology studies in mice, rats, and dogs, Fp's toxic manifestations were characteristic of glucocorticoids (eg, weight loss, decreased thymus weight, and/or decreased cortisol levels). Minimal toxicity and no mortality were observed after very high oral doses (≥1000 mg/kg) in mice and rats, which is likely due to extensive first-pass metabolism.

Salmeterol xinafoate (Sx)

Salmeterol acute toxicology has been evaluated in rats, mice and dogs. No mortality was observed after administering inhalation doses of 2.9 or 0.7 mg/kg to rats or dogs, respectively, or oral doses of 150 or 1000 mg/kg to mice or rats. Mortality was noted in mice after oral administration of salmeterol base at 125 mg/kg.

Fluticasone and Salmeterol Combination

Acute inhalation toxicology studies of Fp and Sx dry powder combinations have been performed in rats and dogs.

The studies in rats included a 1:2 [ratio] combination dose (at a high dose of 1.93 mg/kg Fp and 3.63 mg/kg Sx) that resulted in typical β2-agonist (eg, cardiotoxicity) and glucocorticoid (eg, decreased body weight gain and lymphoid depletion) effects and some local effects (eg, irritation to the larynx and nasal cavity), a 2:1 combination at lower doses (0.46 or 0.91 mg/kg Fp and 0.25 or 0.49 mg/kg Sx) showed similar findings to a lesser degree and no larynx or nasal cavity irritation, a subsequent 2:1 combination (at 1.1 or 5.4 mg/kg Fp and 0.56 or 2.8 mg/kg Sx) showed only atrial myocarditis, which is characteristic of β2-agonism, and a third study that was comprised of a single inhalation dose of Sx alone at 5.2 mg/kg, which was associated with ventricular degeneration, and a combination of Fp at 1.9 mg/kg and Sx at 3.3 mg/kg that produced atrial myocarditis in addition to ventricular degeneration. The latter study suggested the potential for enhanced cardiotoxicity with the combination; however, subsequent repeat-dose toxicology studies suggest the combination is not associated with significant effects on ECG or cardiac histopathology.

A single-dose inhalation toxicology study in dogs at a 1:1 combination (0.016 or 0.164 mg/kg Fp and 0.017 or 0.178 mg/kg Sx) revealed findings characteristic of β2-agonists and glucocorticoids. The low dose showed a decrease (50%) in body weight gain and the high-dose group showed an increased (33%) body weight gain, suggesting the β2 agonist's pharmacological effect (increased body weight gain) offset the decreased body weight gain effect of the glucocorticoid.

2.3.4.2. Repeat dose toxicity

Fluticasone propionate (Fp)

The toxicological profile of Fp is generally characterised by exaggerated glucocorticoid pharmacological activity. Fp at high doses is associated with findings such as lymphoid depletion, decreased cortisosterone levels, decreased body weight gain, increased red blood cell (RBC) counts, and decreased white blood cell (WBC) counts, and liver, adrenal, spleen and thymus histopathology findings in rats; and decreased cortisol response to Synacthen (ACTH), decreased body weight gain, increased urea and cholesterol levels, increased liver weights, decreased adrenal weights, and thymic atrophy in dogs.

Salmeterol xinafoate (Sx)

The observations from repeat-dose toxicology studies conducted in rats and dogs were generally characteristic of β-agonists.

Salmeterol at high enough doses was associated with findings such as reductions in the number of platelets, decreased plasma glucose, increased urea and creatinine, increased urine volume associated with decreased specific gravity, increased heart and lung weights and decreased liver and kidney weights, and skeletal muscle hypertrophy in rats; and tachycardia, vasodilation, hypoglycemia, palpillary muscle fibrosis and calcification, and increased muscle mass in dogs.

Fluticasone and Salmeterol Combination

A battery of repeat dose toxicology studies conducted in rats and dogs have been conducted for Advair Diskus. The combination toxicology studies were not designed such that NOAEL levels for the combination could be determined. Instead, the approach was to give the drugs in combination at doses with known toxic effects to see if toxicity was altered in the presence of the other drug. The findings were generally as expected for the doses of Sx and Fp administered, most being typical of β2-agonist or corticosteroid excess. The repeat dose toxicity studies confirm previous findings that Fp enhances the cardiac toxicity of Sx in rats. The atrial myocarditis and coronary arteritis observed in rats was not observed in dogs. Overall, there was no evidence for synergism, potentiation, or unique effects of the combination.

2.3.4.3. Genotoxicity

No new genetic toxicology studies were conducted for this submission.

Fluticasone Propionate (Fp)

Fp did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the *in vivo* mouse micronucleus test.

Salmeterol Xinafoate

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No clastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test.

Fluticasone and Salmeterol Combination

No genetic toxicology studies could be found with the combination. According to ICH M3, combination genotoxicity studies are not needed when the individual agents have been appropriately tested.

2.3.4.4. Carcinogenicity

No new carcinogenicity studies were conducted for this submission.

Fluticasone Propionate (Fp)

Fp demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg for 78 weeks or in rats at inhalation doses up to 57 mcg/kg for 104 weeks.

Salmeterol Xinafoate (Sx)

In an 18-month carcinogenicity study in CD-mice, Sx at oral doses of 1.4 mg/kg and above caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts. No tumours were seen at 0.2 mg/kg.

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above. No tumours were seen at 0.21 mg/kg. These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Fluticasone and Salmeterol Combination

According to ICH M3 on-clinical safety studies for the conduct of human clinical trials for pharmaceuticals, combination carcinogenicity studies are not needed when the individual agents have been appropriately evaluated.

2.3.4.5. Reproductive and Developmental Toxicity

Fluticasone Propionate (Fp)

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically throughout the period of organogenesis at relatively low-dosage levels; however, when delivered via inhalation to rats, Fp did not induce teratogenicity at a maternal toxic dose.

Cleft palate and fetal skeletal variations were observed in mouse fetuses at a maternal subcutaneous dose of 45 mcg/kg/day. The mouse NOAEL was observed with a dose a maternal subcutaneous dose of 15 mcg/kg/day.

Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a maternal subcutaneous dose of 100 mcg/kg/day. The rat no NOAEL was observed at a maternal subcutaneous dose of 30 mcg/kg/day.

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, Fp produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a maternal inhalation dose of 25.7 mcg/kg/day; however, there was no evidence of teratogenicity. The NOAEL was observed with a maternal inhalation dose of 5.5 mcg/kg/day.

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, Fp produced reductions of fetal body weights, in the presence of maternal toxicity, at a maternal subcutaneous dose of 0.57 mcg/kg/day. Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a a maternal subcutaneous dose of 4 mcg/kg/day. The NOAEL was observed in rabbit fetuses with a maternal subcutaneous dose of 0.08 mcg/kg/day.

Fp crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), Fp was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 50 mcg/kg/day.

Salmeterol Xinafoate (Sx)

β2-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels and may interfere with uterine contractility.

In 2 embryofetal development studies, pregnant rats received Sx by oral administration at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryofetal effects at maternal oral doses up to 10,000 mcg/kg/day.

In 3 embryofetal development studies, pregnant rabbits received oral administration of Sx at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits administered Sx at maternal oral doses of 1,000 mcg/kg/day and higher, fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No such effects occurred at a Sx dose of 600 mcg/kg/day. New Zealand White

rabbits were less sensitive, as only delayed ossification of the frontal cranial bones was observed at a Sx maternal oral dose of 10,000 mcg/kg/day.

In a peri- and post-natal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, Sx at a maternal oral dose of 10,000 mcg/kg/day was fetotoxic and decreased the fertility of survivors. Sx crossed the placenta following oral administration to mice and rats.

No effects on fertility or reproductive performance were identified in rats treated with Sx at oral doses up to 2 mg/kg.

Fluticasone and Salmeterol Combination

In the mouse reproduction assay, Fp by the subcutaneous route at 150 mcg/kg/day combined with oral Sx at 10 mg/kg/day produced cleft palate, fetal death, increased implantation loss, and delayed ossification. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses of Fp subcutaneously up to 40 mcg/kg/day and oral doses of salmeterol up to 1.4 mg/kg/day.

In rats, combining Fp subcutaneously at 100 mcg/kg/day and an oral dose of Sx at 10 mg/kg/day produced decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. No such effects were seen when combining Fp subcutaneously at a dose of 30 mcg/kg/day and an oral dose of salmeterol at 1 mg/kg/day.

2.3.4.6. Juvenile toxicity

Subcutaneous administration of 1, 5 or 10 mcg/kg/day Fp to juvenile rats from day 8-43 of life did not affect survival or general health of treated rats. Male and female animals receiving 10 mcg/kg/day exhibited a reduced rate of body weight gain, but sexual maturation, as assessed by the decent of testes or vaginal opening, was unaffected. Examination of the epiphyses of the femur indicated no major corticosteroid effects on growth. A decrease in thymus weight was seen in animals receiving 5 or 10 mcg/kg/day, but no corresponding histological changes were detected. Based on these findings, it was concluded that fluticasone propionate had no specific effects on the maturation of juvenile rats.

In a juvenile dog study, 5, 15 or 25 mcg/kg/day Fp was administered by head-only inhalation to 2-week-old dogs for 20 minutes per day for 7 weeks. There were no adverse developmental or irritation effects observed in the lungs or other respiratory tract structures among treated dogs. Treatment-related findings were limited to a decrease in body weight gain in male dogs of all groups and macroscopic and microscopic pathological changes in the adrenal glands, including atrophy of the zona fasciculata in the adrenals of males and females receiving 15 or 25 µg/kg/day.

In a separate juvenile dog study, Fp was administered to juvenile dogs by face mask inhalation at doses of 7.2 or 52.6 mcg/kg/day for 5 weeks, findings included a decrease in body weight gain, a marked decrease in plasma cortisol levels, atrophy of the zona fasciculata in the adrenal gland and depletion of lymphocytes in the thymus, which correlated with a decrease in adrenal and thymus weights in animals receiving 52.6 mcg/kg/day.

Similar findings were observed in longer term studies with Fp in dogs. In a 13-week study where juvenile dogs were administered Fp by face mask inhalation at doses of 4, 12 or 29 mcg/kg/day, no treatment related findings in clinical observations, ophthalmoscopic examinations, or in haematology/ clinical chemistry parameters were noted at any dose. There was no evidence of lung developmental impairment. The only effect noted was the slightly lower body weight gain for the high dose females when compared to the controls. Plasma cortisol levels were reduced in the intermediate and high dose

groups in a dose related manner. Postmortem evaluations revealed a reduction in adrenal weights in animals receiving the high dose, and histopathological examination revealed marked atrophy of the zona fasciculata in the adrenal glands of all animals receiving the high dose, with mild atrophy being observed in one intermediate animal. The adrenal findings are consistent with the exaggerated pharmacological responses to corticosteroids.

2.3.4.7. Local tolerance

No local tolerance studies were conducted.

2.3.4.8. Other toxicities studies

Impurities and Degradation Products

All impurities/degradation product specifications are below the ICH Q3A (Impurities in new drug substances) and Q3B (Impurities in new drug products) qualification thresholds for the active substance and finished product, respectively. Therefore, impurities/degradation products should not present a safety concern for FS MDPI.

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of FS Spiromax containing fluticasone propionate and salmeterol xinafoate is considered unlikely to result in any significant increase in the exposure of the environment to the active substance. Moreover, taking into account that the predicted environmental concentration in surface water (PEC_{sw}) for FS PMDI was lower than the PEC_{sw} of approved fluticasone/salmeterol products, no additional Phase 1 and 2 data were deemed necessary to provide as part of this application. Thus, the ERA is expected not to be increased and therefore salmeterol xinafoate/fluticasone propionate is considered unlikely to present a risk to the environment by the applicant.

2.3.6. Discussion on non-clinical aspects

Pharmacology

No new non-clinical pharmacology studies were conducted for fluticasone propionate (Fp), Salmeterol xinafoate (Sx) or the Fluticasone-Salmeterol (FS) combination. This is considered acceptable and in line with the EMA's guideline on the development of fixed dose combinations (EMA/CHM/SWP/258498). A literature review of the pharmacology of the individual components alone and in combination has been presented and is considered acceptable by CHMP.

Comprehensive information on the non-clinical pharmacology of each single agents (salmeterol and fluticasone) or two agents combinations are documented in the published literature. Each of individual components are known to have different mechanism of actions.

Fluticasone propionate is a potent fluorinated glucocorticoid with anti-inflammatory activity that is commonly used to treat asthma and allergic rhinitis. Fluticasone propionate has been marketed in the EU for many years and has been shown to reduce symptoms and exacerbations of asthma and to decrease airway reactivity to histamine and methacholine in patients with hyperreactive airways. Fluticasone propionate is a well-established active substance and is recommended for use in the management of asthma in both adults and adolescents.

Salmeterol xinafoate is a LABA bronchodilator that exerts a preferential effect on β2-adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation that lasts for 12 hours after a single dose. Salmeterol is used via the orally inhaled route in the management of patients with reversible airways obstruction associated with mild to moderate asthma. Salmeterol 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.

The fluticasone propionate/salmeterol (FS) combination is already authorize and indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting β2-agonist) is appropriate: in patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β2-agonist or in patients already adequately controlled on both inhaled corticosteroid and long-acting β2-agonist. FS fixed-dose combination products have been marketed in the EU for over 21 years in dry powder inhalation formulations (e.g. Seretide Diskus).

Overall, CHMP agreed that LABA and ICS may optimise each other's beneficial actions in the airways, and that the low systemic effects of these drugs should not result in any increase in adverse effects.

The secondary pharmacodynamic and safety pharmacology effects of the fluticasone and salmeterol combination are largely predictable from well-defined pharmacology of the two individual agents. The Applicant relied on the literature on non-clinical data concerning secondary pharmacodynamics of the active substances. This was considered acceptable by CHMP. Furthermore, CHMP acknowledged that patients have already been exposed to fluticasone and salmeterol and information on potential effects on the central nervous system, cardiovascular system and respiratory function might be based on clinical data, therefore, the absence of extensive non-clinical data is justified.

Pharmacodynamic drug interactions are described in the relevant sections of the SmPC. The absence of pharmacodynamic interaction animal studies is acceptable by CHMP.

Pharmacokinetics

The pharmacokinetics of fluticasone propionate and salmeterol xinafoate has been well characterised in humans and non-clinical species. No additional new pharmacokinetic animal studies were performed to support this submission. This is considered acceptable by CHMP.

Both fluticasone and salmeterol exert their effects locally in the lung; therefore, plasma levels do not predict therapeutic effect in humans. Fluticasone propionate is associated with low oral bioavailability and considerable pulmonary bioavailability, with most fluticasone propionate delivered to the lung being systemically absorbed. Salmeterol is extensively absorbed after oral and inhalation administration; however, detectable systemic levels are very low because the therapeutic dose is so small. Fluticasone and salmeterol are highly bound to plasma proteins. Both compounds are metabolised through the cytochrome P450 isozyme (CYP) 3A4 pathway. Fluticasone is associated with a rapid and extensive metabolic clearance with rapid elimination in the bile and excretion in feces, while salmeterol and its metabolites are excreted predominantly in the bile. The terminal half-life in humans for both compounds is approximately 5½ hours.

Lactose monohydrate is a well characterize excipient used in the final drug product. This excipient may contain trace amounts of milk protein which may cause reactions in patients with hypersensitivity or allergy to milk protein. In addition, lactose is contraindicated in patients with galactose intolerance, Lapp lactase deficiency or with glucose- galactose malabsorption and patients with these rare hereditary problems should not take this medicine.

Toxicology

No new single dose toxicity studies were conducted by the Applicant for this submission. This is considered acceptable by CHMP. Furthermore, the innovator combination product as well as the individual components is on the market for a period of over 10 years.

Overall, previously single dose toxicity studies conducted individually or in combination demonstrated no specific target organ toxicity.

The currently available non-clinical data for each single agents and in combination, together with the clinical experience with the active substances in FS MDPI and the general use of LABA/ICS combinations in clinical settings do not indicate additional safety concerns for BroPair Spiromax and are therefore considered adequate to support the marketing authorisation application without additional pharmacology studies.

Environmental risk assessment (ERA)

The justification for the absence of an ERA is acceptable and an ERA is not deemed necessary. FS Spiromax is considered unlikely to present a risk to the environment when use as prescribed.

2.3.7. Conclusion on the non-clinical aspects

No new non-clinical studies have been conducted by the applicant which is considered in line with the EMA's guideline on the development of fixed dose combinations and acceptable by CHMP. The pharmacological, pharmacokinetic and toxicological aspects of fluticasone and salmeterol have been extensively studied and are well characterised. The results of the non-clinical data are appropriately described in the SmPC section 5.3.

2.4. Clinical aspects

2.4.1. Introduction

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.

- Tabular overview of clinical studies

The clinical development programme for BroPair Spiromax comprised 9 studies which included:

- 2 Phase 1 studies for early formulation decisions (**FpS-AS-101** and **FpS-AS-102**);

- 3 Phase 2 dose-ranging studies (**FpS-AS-201**, **FpS-AS-202**, and **FSS-AS-201**) to confirm selections of 3 Fp dose strengths and the salmeterol dose for Phase 3;

- 1 single pharmacokinetic study that was conducted later in the programme to confirm systemic exposure with the final formulation (**FSS-AS-10042**);

- 3 Phase 3 studies including 2 replicated placebo-controlled efficacy and safety studies (**FSS-AS-301** and **FSS-AS-30017**) and a single open-label active-controlled, long-term safety study (**FSS-AS-305**).

Table 1: Overview of clinical studies

Study identifier (type of study) Total number of centres with enrolled subjects Country(ies)	Objective(s) of the study	Study design and type of control	Test product(s) Dosage regimen Route of administration	Number of subjects Treated and Completed study M/F (enrolled) Age range (y)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
Phase 1 Pharmacokinetics, Safety, and Tolerability							
FpS-AS-101 (Pharmacokinetic) 1 site US	To assess the pharmacokinetic profiles of single doses of Fp administered as 2 inhalations from Fp MDPI 400 mcg and 4 inhalations from FLOVENT DISKUS 250 mcg and 4 inhalations from FLOVENT HFA MDI 220 mcg	Randomised, single-centre, open-label, 3-period crossover, single-dose	Fp MDPI 400 mcg nominal dose 2 inhalations FLOVENT DISKUS 250 mcg metered dose 4 inhalations FLOVENT HFA MDI 220 mcg delivered dose 4 inhalations	Treated: 18 Completed: 17 M 8/F 10 23-44 y	Healthy volunteers	Single-dose	Completed Full CSR (Module 5.3.3.1)
FpS-AS-102 (Pharmacokinetic) 1 site US	To assess the pharmacokinetic profiles of single doses of Fp administered as 4 inhalations from Fp MDPI 100 and 200 mcg and 4 inhalations from FLUTIDE DISKUS 100 mcg in healthy Japanese and matched Caucasian subjects	Randomised, open-label, 3-period crossover, single-dose	Fp MDPI 100 mcg nominal dose 4 inhalations 200 mcg nominal dose 4 inhalations FLUTIDE DISKUS 100 mcg metered dose 4 inhalations	Treated: 30 Completed: 30 M 20/F 10 22-45 y	Healthy, matched, Japanese and Caucasian volunteers	Single-dose	Completed Full CSR (Module 5.3.3.1)

Study identifier (type of study) Total number of centres with enrolled subjects Country(ies)	Objective(s) of the study	Study design and type of control	Test product(s) Dosage regimen Route of administration	Number of subjects Treated and Completed study M/F (enrolled) Age range (y)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
FSS-AS-10042 (Pharmacokinetic) 3 sites US	To determine the pharmacokinetic profiles of fluticasone propionate and/or salmeterol from a single dose of Fp MDPI 200 mcg and FS MDPI 232/14 mcg as compared with FLOVENT DISKUS (GlaxoSmithKline) 500 mcg or ADVAIR DISKUS (GlaxoSmithKline) 500/50 mcg	Randomised, multicentre, open-label, 4-period crossover, single-dose	Fp MDPI 200 mcg nominal dose 1 inhalation FS MDPI 200/12.5 mcg nominal dose 1 inhalation FLOVENT DISKUS 250 mcg metered dose 2 inhalations ADVAIR DISKUS 500/50 mcg metered dose 1 inhalation	Treated: 40 Completed: 38 M 24/F 19 12-72 y	Patients with persistent asthma	Single-dose	Completed Full CSR (Module 5.3.3.1)
Phase 2 Dose Ranging							
FpS-AS-201 (Safety and Efficacy) 188 sites US, Israel, Spain, Poland, Ukraine, Hungary, Croatia, Serbia, and Bulgaria	To evaluate the dose response, efficacy, and safety of 4 different doses of fluticasone propionate (12.5, 25, 50, and 100 mcg) delivered as Fp MDPI	Randomised, double-blind, placebo- and open-label active-controlled, parallel-group, multicentre, dose-ranging	Fp MDPI 12.5 mcg nominal dose 1 inhalation twice a day 25 mcg nominal dose 1 inhalation twice a day 50 mcg nominal dose 1 inhalation twice a day 100 mcg nominal dose 1 inhalation twice a day FLOVENT DISKUS 100 mcg metered dose 1 inhalation twice a day Placebo MDPI 1 inhalation twice a day	Treated: 622 Completed: 483 M 264/F 358 12-81	Patients with persistent asthma who are uncontrolled on nonsteroidal therapy	12 weeks	Completed Full CSR (Module 5.3.5.1)

Study identifier (type of study) Total number of centres with enrolled subjects Country(ies)	Objective(s) of the study	Study design and type of control	Test product(s) Dosage regimen Route of administration	Number of subjects Treated and Completed study M/F (enrolled) Age range (y)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
FpS-AS-202 (Safety and Efficacy) 180 sites US, Canada, Ukraine, Hungary, Germany, Israel, Romania, Bulgaria, Poland, Spain, Greece, New Zealand, Croatia, and Serbia	To evaluate the dose response, efficacy, and safety of 4 different doses of fluticasone propionate (50, 100, 200, and 400 mcg) delivered as Fp MDPI	Randomised, double-blind, placebo- and open-label active-controlled, parallel-group, multicentre, dose-ranging	Fp MDPI 50 mcg nominal dose 1 inhalation twice a day 100 mcg nominal dose 1 inhalation twice a day 200 mcg nominal dose 1 inhalation twice a day 400 mcg nominal dose 1 inhalation twice a day FLOVENT DISKUS 250 mcg metered dose 1 inhalation twice a day Placebo MDPI 1 inhalation twice a day	Treated: 639[a] Completed: 459 M 261/F 379 12-83	Patients with severe persistent asthma who remain symptomatic despite high-dose ICS therapy	12 weeks	Completed Full CSR (Module 5.3.5.1)
FSS-AS-201 (Safety and Efficacy) 10 sites US	To evaluate the dose response, efficacy, and safety of 4 different doses of salmeterol xinafoate (6.25, 12.5, 25, and 50 mcg) each combined with a fixed dose of fluticasone propionate (100 mcg) delivered as FS MDPI	Randomised, multicentre, double-blind and open-label active-controlled, single-dose, 6-period crossover, dose-ranging	FS MDPI 100/6.25 mcg nominal dose 1 inhalation 100/12.5 mcg nominal dose 1 inhalation 100/25 mcg nominal dose 1 inhalation 100/50 mcg nominal dose 1 inhalation Fp MDPI 100 mcg nominal dose 1 inhalation ADVAIR DISKUS 100/50 mcg metered dose 1 inhalation	Treated: 72 Completed: 65 M 35/F 37 13-86 y	Patients with persistent asthma who are controlled on ICS and SABA therapy at study entry	Single-dose	Completed Full CSR (Module 5.3.3.2)

Study identifier (type of study) Total number of centres with enrolled subjects Country(ies)	Objective(s) of the study	Study design and type of control	Test product(s) Dosage regimen Route of administration	Number of subjects Treated and Completed study M/F (enrolled) Age range (y)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
Phase 3 Long-Term Comparison and Safety							
FSS-AS-305 (Safety) 103 sites[a] US	To evaluate the long-term safety of fluticasone propionate inhalation powder in 2 strengths and Fp/FS inhalation powder in 2 strengths when administered with the Teva MDPI device	Randomised, open-label, active-controlled	Fp MDPI 100 mcg nominal dose 1 inhalation twice a day 200 mcg nominal dose 1 inhalation twice a day FLOVENT HFA 110 mcg delivered dose 2 inhalations twice a day 220 mcg delivered dose 2 puffs twice a day FS MDPI 100/12.5 mcg nominal dose 1 inhalation twice a day 200/12.5 mcg nominal dose 1 inhalation twice a day ADVAIR DISKUS 250/50 mcg metered dose 1 inhalation twice a day 500/50 mcg metered dose 1 inhalation twice a day	Treated: 673 Completed: 595 M 266/F 406 (sex not reported for 2 patients) 12-79 y	Patients with persistent asthma and who are currently being treated with mid-dose or high-dose ICS or ICS/LABA as their daily controller	26 weeks	Completed Full CSR (Module 5.3.5.2)

Study identifier (type of study) Total number of centres with enrolled subjects Country(ies)	Objective(s) of the study	Study design and type of control	Test product(s) Dosage regimen Route of administration	Number of subjects Treated and Completed study M/F (enrolled) Age range (y)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
Phase 3 Confirmatory Efficacy							
FSS-AS-301 (Efficacy and Safety) 129 sites[a] US, Canada, Poland, Russia, South Africa, Ukraine, and Hungary	To evaluate the efficacy of Fp MDPI and FS MDPI	Randomised, double-blind, parallel-group, placebo-controlled	Fp MDPI 50 mcg nominal dose 1 inhalation twice a day 100 mcg nominal dose 1 inhalation twice a day FS MDPI 50/12.5 mcg nominal dose 1 inhalation twice a day 100/12.5 mcg nominal dose 1 inhalation twice a day Placebo MDPI 1 inhalation twice a day	Treated: 641 Completed: 602 M 283/F 364 12-86 y	Adolescent and adult patients with persistent asthma, symptomatic despite low-dose or mid-dose ICS therapy	12 weeks	Completed Full CSR (Module 5.3.5.1)
FSS-AS-30017 (Efficacy and Safety) 147 sites[a] US, Canada, Czech Republic, Hungary, Poland, Russia, South Africa, and Ukraine	To evaluate the efficacy of Fp MDPI and FS MDPI	Randomised, double-blind, parallel-group, placebo-controlled	Fp MDPI 100 mcg nominal dose 1 inhalation twice a day 200 mcg nominal dose 1 inhalation twice a day FS MDPI 100/12.5 mcg nominal dose 1 inhalation twice a day 200/12.5 mcg nominal] dose 1 inhalation twice a day Placebo MDPI 1 inhalation twice a day	Treated: 723 Completed: 650 M 289/F 439 12-84 y	Adolescent and adult patients with persistent asthma, symptomatic despite mid-dose or high-dose ICS or ICS/LABA therapy	12 weeks	Completed Full CSR (Module 5.3.5.1)

a Represents number of sites that screened at least 1 patient. CSR=clinical study report; F=female; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; HFA=hydrofluoroalkane; ICS=inhaledgcp corticosteroid; LABA=long-acting β2-agonist; M=male; MDI=metered-dose inhaler; MDPI=multidose dry powder inhaler; SABA=short-acting β2-agonist; US=United States.

2.4.2. Pharmacokinetics

The clinical pharmacology programme for BroPair Spiromax (FS MDPI) included studies to characterise the pharmacokinetics (PK) of Fp and/or salmeterol after single-dose oral inhalation administration. This application relied, in part, on the previously demonstrated PK and safety of Advair Diskus and Seretide Accuhaler.

The intent of the PK studies was to characterise the PK of the FS MDPI and to compare the exposure of Fp and/or salmeterol administered from FS MDPI with administration from Advair Diskus. To this end, the applicant conducted 2 clinical studies with FS MDPI that included PK evaluation (Study **FSS-AS-10042** and Study **FSS-AS-201**). These studies used a matched number of inhalations for administration using the FS MDPI and Advair Diskus inhalers. Furthermore, the **FSS-AS-10042** study used the final version of the FS MDPI device/formulation, which was identical to that used in the Phase 3 studies. Study FSS-AS-10042 was a single-dose, crossover study. It compared the PK profiles of FS MDPI and Advair Diskus in patients with persistent asthma. The study also included comparison of Fp MDPI and Flovent Diskus.

In addition to the PK study of FS MDPI, PK studies of Fp MDPI with a comparator (Flovent Diskus) were also performed. The Fp MDPI device is identical to the FS MDPI device but delivers Fp alone. As such, the PK data for Fp delivered from the Teva Fp MDPI device is included in this submission as supportive only (the mono-component Fp was not submitted for approval in the EU).

Two Phase 2 studies included an evaluation of the PK of Fp delivered from the MDPI device (Studies **FpS-AS-201** and **FpS-AS-202**), and one Phase 2 study included an evaluation of the PK of salmeterol delivered from the MDPI device (**FSS-AS-201**). Each of these studies also included a comparator (either Flovent Diskus or Advair Diskus, as appropriate).

The oral bioavailability of Fp is approximately 0% due to extensive first-pass metabolism. Salmeterol systemic exposure is partly attributable to oral absorption. However, the studies with FS MDPI did not include a treatment arm with charcoal administration for oral drug removal. Instead, a post-hoc analysis of salmeterol area under the plasma concentration time curve from time 0 to 30 minutes post-dose ($AUC_{0\text{-}30min}$) was conducted as this is an acceptable surrogate of efficacy related exposure for drugs that are rapidly absorbed via the lungs (maximum observed plasma concentration [Cmax] occurring within 5 minutes or less), such as salmeterol.

Fluticasone propionate (Fp)

In Study **FSS-AS-10042,** after administration of Fp via the FS MDPI device, plasma Fp levels exhibited a time to maximum plasma concentration (t_{max}) ranging from 1 to 2 hours. After reaching peak levels, Fp subsequently declined in a multiphasic manner. The elimination half-life ($t_{½}$) was approximately 10 hours. Plasma concentrations of Fp peaked between 0.5 and 4 hours after treatment. Upon reaching peak levels, Fp concentrations decreased in a multiphasic manner. Comparisons between FS MDPI and Advair Diskus showed that the ratio of geometric LS means was close to unity for exposure parameters. All exposure parameters for FS MDPI/Advair Diskus comparisons had their 90% CI contained within the 80% to 125% boundaries.

Dose proportionality of $AUC_{0\text{-}t}$ and C_{max} for Fp was evaluated in an exploratory manner by application of a power model to data obtained with Fp MDPI from **Study FpS-AS-201** and **Study FpS-AS-202** (summary of PK results in both studies is presented below). Over a nominal dose range (12.5 to 400 mcg) of Fp MDPI, the increases in Fp $AUC_{0\text{-}t}$ were approximately dose proportional while those for Cmax were slightly less than dose proportional. For the Fp MDPI 50, 100, and 200 mcg nominal doses, both PK parameters for Fp increased in an approximately dose proportional manner, as indicated by 90% CI of the slopes that generally contained unity. This outcome is consistent with the in vitro proportionality of the delivered and aerodynamic performance between the 3 strengths.

In both studies, exposure (as assessed by area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration [AUC0-t] and maximum observed plasma concentration [Cmax]) increased in proportion to the increasing dose of Fp MDPI. The Fp MDPI 50 mcg strength corresponds to the low strength of FS MDPI (50/12.5 mcg) included in this application. The results from these studies were supportive of the studies with FS MDPI where the exposure of Fp administered from FS MDPI increased with increasing doses in the same manner.

PK of Fp after multiple administrations were not studied in this programme. Although some accumulation is predicted to occur following bid administration of Fp and salmeterol, on the basis of the single-dose profiles, the PK are expected to be linear. The systemic exposures are expected to be lower to the systemic exposure after repeat administration of Advair Diskus or Seretide Accuhaler.

Study FpS-AS-201: summary of PK results

Fp $AUC_{0\text{-}t}$ and C_{max} increased with increasing dose of Fp MDPI. The t_{max} was similar across treatments (median t_{max} ranged from 0.8 through 1.1 hours).

Table 2: Plasma Pharmacokinetic Parameters for Fluticasone Propionate (Study FpS-AS-201)

Parameter	Fp MDPI				FLOVENT DISKUS 100 mcg (N=21)
	12.5 mcg (N=16)	25 mcg (N=22)	50 mcg (N=19)	100 mcg (N=17)	
Mean (SD) AUC_{0-t} (pg•h/mL)	21.6 (27.09)	42.0 (23.21)	63.2 (22.64)	153.8 (91.42)	103.4 (45.65)
Mean (SD) C_{max} (pg/mL)	5.4 (4.23)	10.0 (5.35)	12.9 (5.13)	33.6 (15.49)	23.4 (10.73)
Median (min, max) t_{max} (h)	1.1 (0.2, 4.0)	1.0 (0.1, 12.0)	1.0 (0.3, 12.0)	0.8 (0.2, 4.0)	1.0 (0.3, 12.0)

Source: FpS-AS-201 clinical study report, Table 27.

AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; C_{max}=maximum observed plasma concentration; Fp MDPI=fluticasone propionate multidose dry powder inhaler; max=maximum; min=minimum; N=total number of patients in the group; SD=standard deviation; t_{max}=time to maximum observed concentration.

Note: Actual time for AUC_{0-t} was 0 to 12 hours.

This study assessed Fp exposure after Fp MDPI single doses of 12.5 mcg, 25 mcg, 50 mcg, and 100 mcg in a parallel-group design. Exposure (as assessed by AUC_{0-t} and C_{max}) increased in a dose proportional manner with increasing doses of Fp MDPI. The 50mcg dose of Fp in the Fp MDPI 50 mcg strength corresponds to the Fp dose in the low strength of FS MDPI (50/12.5 mcg) included in this application. The exposure parameters of Fp after administration from FS MDPI are expected to increase similarly with dose, since the device used is the same as Fp MDPI and the Fp exposure was similar when the higher strength (200 mcg) of Fp MDPI and FS MDPI was compared (Study FSS-AS-10042).

Overall, Fp systemic exposure (both area under the plasma drug concentration-time curve from time 0 to the time of the last measurable drug concentration [AUC0-t] and maximum observed plasma concentration [Cmax]) was higher for Fp MDPI (100 mcg bid) than Flovent Diskus (100 mcg bid), reflecting better efficiency of delivery from the MDPI device. In addition, Fp systemic exposure (both AUC0-t and Cmax) was lower for both 25 and 50 mcg bid Fp MDPI doses compared with 100 mcg bid Flovent Diskus.

Study FpS-AS-202: summary of PK results

Systemic exposure (both AUC0-t and Cmax) to Fp was higher for Fp MDPI (200 and 400 mcg bid) than Flovent Diskus (250 mcg bid). However, the differences in exposure parameters for Fp MDPI (400 mcg bid) relative to Flovent Diskus (250 mcg bid) were within 2-fold. Systemic exposure (both AUC0-t and Cmax) to Fp was lower for both the 50 and 100 mcg bid Fp MDPI doses compared with 250 mcg bid Flovent Diskus.

The t_{max} was similar across treatments.

Table 3: Fluticasone Propionate Pharmacokinetics Descriptive Statistics (Study FpS-AS-202)

Parameter Statistic	Fp MDPI				FLOVENT DISKUS 250 mcg (N=16)
	50 mcg (N=18)	100 mcg (N=18)	200 mcg (N=18)	400 mcg (N=20)	
Mean (SD) AUC_{0-t} (pg•h/mL)	117.6 (145.79)	126.8 (33.73)	292.0 (162.28)	462.8 (262.45)	162.3 (74.79)
Mean (SD) C_{max} (pg/mL)	19.1 (15.53)	26.5 (6.18)	55.2 (29.12)	83.0 (44.32)	32.5 (13.92)
Median (min, max) t_{max} (h)	1.0 (0.2, 2.0)	0.9 (0.2, 8.0)	1.1 (0.3, 12.0)	0.8 (0.1, 12.0)	1.1 (0.5, 12.0)

Source: FpS-AS-202 clinical study report, Table 27.

AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; C_{max}=maximum observed plasma concentration; Fp MDPI=fluticasone propionate multidose dry powder inhaler; max=maximum; min=minimum; N=total number of patients in the group; SD=standard deviation; t_{max}=time to maximum observed plasma concentration.

Note: Actual time for AUC_{0-t} was 0 to 12 hours.

The exposure (as assessed by AUC_{0-t} and C_{max}) increased with increasing Fp MDPI dose, using a parallel-group design. Fluticasone administered from FS MDPI is expected to increase with increasing doses in the same manner because it is the same device as Fp MDPI and has been shown to result in similar PK when the same dose of Fp is administered from either product.

Salmeterol

After administration of salmeterol via FS MDPI or Advair Diskus, plasma salmeterol levels exhibited a rapid rise with maximal concentrations occurring approximately 0.08 to 2 hours after dosing and subsequently declined in a multiphasic manner. The elimination $t_{½}$ was approximately 12 hours.

Dose proportionality of AUC0-t and Cmax for salmeterol was evaluated in an exploratory manner by application of a power model to data from Study **FSS-AS-201** (a summary of the PK results is presented below). Over a nominal dose range of FS MDPI 100/**6.25** to 100/**50** mcg, the increases in salmeterol AUC0-t and Cmax were slightly greater than dose proportional. Between the FS MDPI 100/**6.25** to 100/**25** mcg nominal doses, both PK parameters for salmeterol increased in a dose proportional manner, as indicated by 90% CI of the slopes that contain unity. This outcome is consistent with the *in vitro* proportionality of the delivered and aerodynamic performance between the 3 strengths.

Post-hoc analyses of salmeterol area under the plasma concentration-time curve from time 0 to 30 minutes post-dose ($AUC_{0-30min}$) were conducted. This is considered to be a surrogate for efficacy. The overall ratio of exposure for FS MDPI versus Advair Diskus was about 77% to 85% for the partial exposure $AUC_{0-30min}$. The total systemic exposure (AUC_{0-t}), however, represents a surrogate for safety; the ratio of FS MDPI versus Advair Diskus was about 50% for the total exposure.

Notably, while the safety exposure is only half that of Advair Diskus, the applicant considered that the targeted exposure to the lungs, resulting in a clinical effect, is 77% to 85% of Advair Diskus.

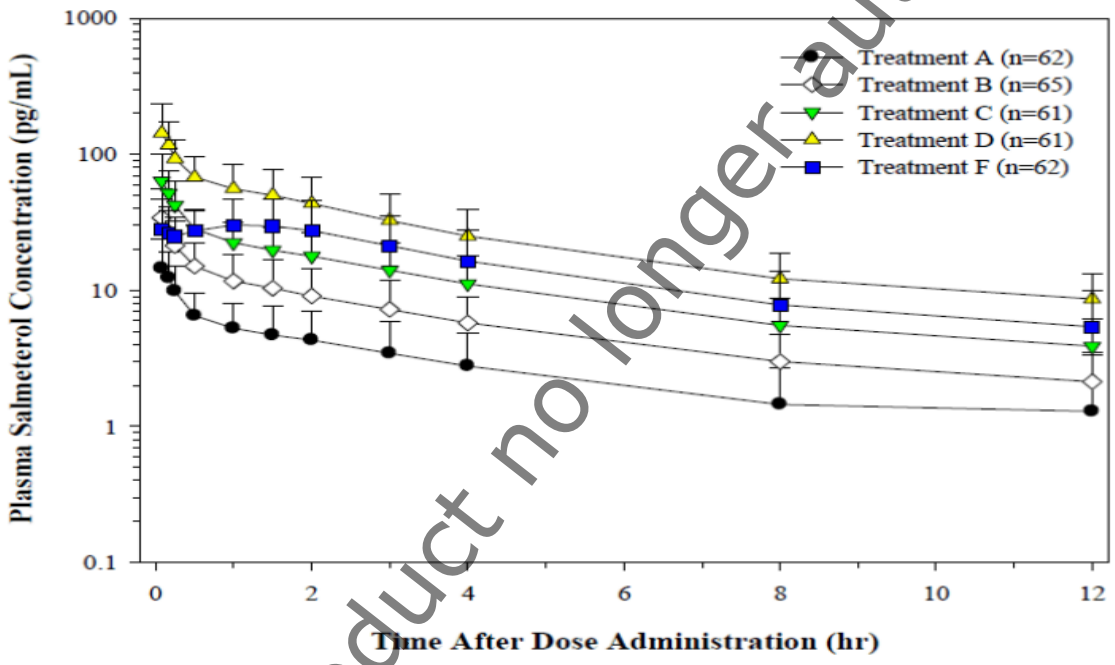
PK of salmeterol after multiple administrations from FS MDPI were not studied in this programme but are expected to be lower to the systemic exposure after repeat administration of Advair Diskus or Seretide Accuhaler.

Study FSS-AS-201: Summary of PK results

The plasma concentration-versus-time profiles of salmeterol after administration from FS MDPI at 100/6.25, 100/12.5, 100/25, and 100/50 mcg and from Advair Diskus 100/50 mcg in patients with asthma are illustrated in Figure 5.

The mean plasma concentrations of salmeterol were highest at 5 minutes after treatment for each FS MDPI dose level. Thereafter, the mean plasma concentrations of salmeterol declined, but were still quantifiable through 12 hours (the last time point sampled) after treatment. There was a dose-related increase in the mean plasma concentrations of salmeterol across the range of FS MDPI doses evaluated.

Figure 5: Plasma Concentration (Mean+Standard Deviation) Versus Time Profiles of Salmeterol after Treatment with FS MDPI Formulations and Advair Diskus (Study FSS-AS-201)



Source: FSS-AS-201 clinical study report, Figure 5.
Treatment A=FS MDPI 100/6.25 mcg.
Treatment B=FS MDPI 100/12.5 mcg.
Treatment C=FS MDPI 100/25 mcg.
Treatment D=FS MDPI 100/50 mcg.
Treatment F=ADVAIR DISKUS 100/50 mcg.

The PK parameters for salmeterol after administration of FS MDPI and Advair Diskus are summarised in Table 4. Both AUC 0-t and C max of salmeterol increased with increasing FS MDPI doses. Across all FS MDPI groups, t max occurred earlier (median=0.1 hour) compared with Advair Diskus (median=0.5 hour).

Table 4: Plasma Pharmacokinetic Parameters of Salmeterol after Administration of FS MDPI or Advair Diskus (Study FSS-AS-201)

Parameter	FS MDPI				ADVAIR DISKUS 100/50 mcg (N=62)
	100/6.25 mcg (N=62)	100/12.5 mcg (N=65)	100/25 mcg (N=61)	100/50 mcg (N=61)	
Mean (SD) AUC_{0-t} (pg•h/mL)	32.8 (21.0)	**69.9 (35.4)**	133.5 (63.1)	309.3 (143.4)	173.5 (106.6)
Mean (SD) $AUC_{0-30min}$ (pg•h/mL)	4.7 (2.41)	**10.6 (5.21)**[a]	20.4 (9.08)	45.8 (19.0)[b]	12.1 (4.74)
Mean (SD) C_{max} (pg/mL)	16.0 (8.9)	**35.8 (20.3)**	67.5 (34.7)	154.5 (80.3)	42.3 (19.3)
Mean (SD) $C_{max, 0-30min}$ (pg/mL)	15.8 (8.95)	**36.1 (20.2)**[a]	67.4 (34.8)	153.4 (81.6)[b]	36.5 (16.7)
Median (min, max) t_{max} (h)	0.1 (0.1, 12.1)	**0.1 (0.1, 2.0)**	0.1 (0.1, 2.0)	0.1 (0.1, 1.5)	0.5 (0.1, 2.0)

Source: FSS-AS-201 clinical study report, Table 18 and FSS-AS-201 MAA Adhoc 5 (xs201ppkx.sas).

[a] n=64

[b] n=60

$AUC_{0-30min}$=area under the plasma concentration-time curve from time 0 to 30 minutes postdose; AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; C_{max}=maximum observed plasma concentration; $C_{max, 0-30min}$=maximum observed plasma concentration in the first 30 minutes after administration; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; max=maximum; min=minimum; N=total number of patients in the group; SD=standard deviation; t_{max}=time to maximum observed concentration.

Note: Actual time for AUC_{0-t} was 0 to 12 hours.

Differences between the FS MDPI doses and the Advair Diskus group for AUC_{0-t} and C_{max} were analysed using an analysis of variance with fixed effects of sequence, period, and treatment (Table 5). Only the FS MDPI 100/50 mcg dose demonstrated a geometric mean ratio (GMR) that was greater than 1 for AUC_{0-t} when compared with Advair Diskus, with all other FS MDPI doses showing ratios that were less than 1. For the C_{max}, the FS MDPI 100/50 and 100/25 mcg doses showed a GMR greater than 1 whereas the ratios for the FS MDPI 100/12.5 and 100/6.25 mcg doses were less than 1.

Table 5: Treatment Comparison of Pharmacokinetic Parameters for Salmeterol Between FS MDPI Dose Groups and Advair Diskus 100/50 mcg (Study FSS-AS-201)

Parameter	n	GMR	90% CI
AUC_{0-t} (pg•h/mL)			
FS MDPI 100/50 mcg vs. ADVAIR DISKUS	58	1.929	1.690, 2.202
FS MDPI 100/25 mcg vs. ADVAIR DISKUS	59	0.800	0.702, 0.911
FS MDPI 100/12.5 mcg vs. ADVAIR DISKUS	**61**	**0.427**	**0.376, 0.485**
FS MDPI 100/6.25 mcg vs. ADVAIR DISKUS	59	0.172	0.151, 0.196
C_{max} (pg/mL)			
FS MDPI 100/50 mcg vs. ADVAIR DISKUS	58	3.622	3.149, 4.168
FS MDPI 100/25 mcg vs. ADVAIR DISKUS	59	1.534	1.335, 1.763
FS MDPI 100/12.5 mcg vs. ADVAIR DISKUS	**61**	**0.795**	**0.694, 0.911**
FS MDPI 100/6.25 mcg vs. ADVAIR DISKUS	59	0.339	0.295, 0.390

Source: FSS-AS-201 clinical study report, Table 19.

AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; CI=confidence interval; C_{max}=maximum observed plasma concentration; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; GMR=geometric mean ratio; n=number of subjects.

Note: Actual time for AUC_{0-t} was 0 to 12 hours.

The applicant considered that the PK evaluation of FS MDPI showed that following administration with Advair Diskus 100/50 mcg, systemic exposure to salmeterol (AUC_{0-t} and C_{max}) was higher than following administration with the FS MDPI 100/12.5 mcg strength and lower strengths of salmeterol, while exposure with Advair Diskus 100/50 mcg was lower than following administration of the FS MDPI 100/25 mcg strength and the higher strengths of salmeterol. Both AUC_{0-t} and C_{max} of salmeterol increased with increasing FS MDPI doses. Although overall systemic exposure (AUC_{0-t}) with FS MDPI 100/12.5 mcg was approximately 43% that of Advair Diskus, in a post-hoc analysis the partial exposure representing lung absorption systemic exposure ($AUC_{0-30\ min}$) for FS MDPI 100/12.5 mcg was approximately 85% that of Advair Diskus.

A discussion was provided on the concept of similarity of systematic exposure to salmeterol between FS MDPI and Advair Diskus, when a geometric mean ratio (GMR) of 0.427 for AUC_{0-t} and 0.795 for the C_{max}, was observed with the comparison of the dose selected for the Phase 3 studies FS MDPI 100/12.5 and Advair Diskus 100/50mcg. Of note, the 100/50mcg dose inhalation powder is the lowest of the three strengths approved for Advair Diskus.

The treatment comparison of FS MDPI 100/12.5 mcg to Advair Diskus 100/50 mcg for salmeterol for area under the plasma concentration-time curve from time 0 to 30 minutes postdose (AUC0-30min) and maximum observed plasma drug concentration in the first 30 minutes after administration (C_{max}, 0-30min) resulted in GMRs of 0.848 pg•h/mL and 0.925 pg/mL, respectively. The data demonstrated that partial exposure for salmeterol, which is a surrogate for efficacy, is comparable between the FS MDPI dose of 100/12.5 mcg and Advair Diskus dose of 100/50 mcg. The Applicant concluded that the clinical data demonstrated a dose response for the range of salmeterol doses tested in the Phase 2 Study FSS-AS-201 that were specifically designed to select the most optimal dose of salmeterol.

Relative Bioavailability from FS MDPI as Compared with Advair Diskus

No formal relative bioavailability studies were performed with FS MDPI. However, systemic exposure was compared between FS MDPI and Advair Diskus.

At comparable doses, systemic exposure was higher for both Fp and salmeterol after administration of FS MDPI low-, mid-, and high-dose strengths compared to Advair Diskus. Therefore, the applicant

developed FS MDPI products at lower doses/strengths (delivered doses 50/12.5, 100/12.5, and 200/12.5 mcg) than Advair Diskus/Seretide Accuhaler (100/50, 250/50, and 500/50 mcg); as those give lower systemic exposures of both Fp and salmeterol than the corresponding Advair Diskus/Seretide Accuhaler doses/strengths.

The PK properties following administration with the combination inhaler, FS MDPI, were compared to that of the Advair Diskus inhaler. The systemic exposure of Fp and salmeterol after administration of FS MDPI relative to the Advair Diskus was evaluated from PK analyses in patients with asthma conducted with the "to be marketed formulation" in the Teva Phase 1 clinical Study **FSS-AS-10042**. It was shown that the highest proposed dose of FS MDPI (**200/12.5** mcg) resulted in similar systemic exposure of Fp and lower systemic exposure of salmeterol than the highest marketed dose of Advair Diskus or Seretide Accuhaler (500/50 mcg).

Although this study included a comparison of high- strength FS MDPI (200/12.5 mcg) to both Advair Diskus and Flovent Diskus, the comparison to Flovent Diskus is less directly comparable, since 2 inhalations were used to administer the dose with the Flovent Diskus inhaler, whereas the high-dose strength was administered with 1 inhalation for both the FS MDPI and Advair Diskus inhalers.

Post-hoc analyses of the dose-ranging Study **FSS- AS-201** and PK Study **FSS-AS-10042**, however, showed that $AUC_{0\text{-}30min}$ for Fp and salmeterol from FS MDPI 200/12.5 mcg was approximately 77% that of Advair Diskus. The ratio of geometric LS mean $AUC_{0\text{-}30min}$ between FS MDPI and Advair Diskus showed that salmeterol exposure from FS MDPI 200/12.5 mcg was approximately 23% lower than from Advair Diskus 500/50 mcg. Although the overall systemic exposure with FS MDPI was only about 50% of Advair Diskus, the effective dose delivered to the site of action, the lungs, was approximately 77% of Advair Diskus.

Based on *in vitro* and *in vivo* dose proportionality observed across strengths of the 2 products, the applicant considered that the low, mid-, and high-dose strength FS MDPI are expected to give lower systemic exposures and similar lung exposures to Fp and salmeterol than the corresponding low-, mid-, and high-dose strengths of Advair Diskus.

Bioequivalence

No formal bioequivalence studies were conducted with FS MDPI. Since the FS MDPI clinical programme demonstrated efficacy and safety with replicate Phase 3 randomised control studies, bioequivalence was not assessed by the applicant. However, the systemic PK of FS MDPI has been compared to Advair Diskus.

Dose proportionality and time dependencies

Fluticasone Propionate (Fp)

There is a linear increase in systemic exposure with increasing inhaled dose for Fp.

There is no information regarding dose-proportionality of Fp exposure from FS MDPI. However, the dose-proportionality of Fp exposure has been evaluated in an exploratory manner for the identical Fp MDPI device. For Fp MDPI, the increase in exposure for Fp for both C_{max} and $AUC_{0\text{-}t}$ was approximately proportional to dose for 50, 100, and 200 mcg across Studies **FpS-AS-201** and **FpS-AS-202**.

The same device is used for the FS MDPI and the Fp MDPI. After administration of Fp via the applicant's Fp MDPI or the Advair Diskus devices, plasma Fp levels exhibited a rise with maximal concentrations occurring approximately 1 to 2 hours after dosing and subsequently declined in a multiphasic manner. The $t_{½}$ was approximately 10 hours.

Dose proportionality of AUC_{0-t} and C_{max} for Fp was evaluated in an exploratory manner by application of a power model to data from Study **FpS-AS-201** and Study **FpS-AS-202** (Table 6).

Table 6: Fluticasone Propionate Dose Proportionality for Fp MDPI (Studies FpS-AS-201 and FpS-AS-202)

Doses	Parameter	Estimated slope for ln(dose)	Standard error	90% CI	
				Lower	Upper
12.5, 25, 50, 100, 200, and 400 mcg	AUC_{0-t}	0.9212	0.0610	0.820	1.022
	C_{max}	0.8191	0.0503	0.736	0.902
50, 100, and 200 mcg	AUC_{0-t}	0.9360	0.1223	0.733	1.139
	C_{max}	0.9451	0.1040	0.772	1.118

Source: FpS-AS-201, Listings 15.2.8.14 and 15.2.8.15 and FpS-AS-202, Listings 16.2.8.15 and 16.2.8.17.
AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; CI=confidence interval; C_{max}=maximum observed plasma concentration; Fp MDPI=fluticasone propionate multidose dry powder inhaler.
Note: The power model, ln (parameter) = a + b×ln (dose) + error, was used to estimate the slope and corresponding 90% confidence interval.
Note: Actual time for AUC_{0-t} was 0 to 12 hours.

In addition, this was consistent with the *in vitro* proportionality of the delivered and aerodynamic performance between the 3 strengths, Fp MDPI 50, 100, and 200 mcg.

Over the whole dose range of Fp MDPI 12.5 to 400 mcg, the increases in Fp AUC 0-t were approximately dose proportional while those for C_{max} were slightly less than dose proportional. For the proposed strengths of Fp MDPI (**50**, **100**, and **200 mcg**), PK parameters for Fp increased in an approximately dose proportional manner, as indicated by 90% CI of the slopes that contain unity.

Salmeterol

After administration of salmeterol via FS MDPI or Advair Diskus, plasma salmeterol levels exhibited a rise with maximal concentrations occurring approximately 0.08 to 2 hours after dosing and subsequently declined in a multiphasic manner. The $t_{½}$ was approximately 12 hours.

Dose proportionality of AUC_{0-t} and C_{max} for salmeterol was evaluated in an exploratory manner by application of a power model to data from Study FSS-AS-201 (Table 7)

Table 7: Salmeterol Dose Proportionality for FS MDPI (Study FSS-AS-201)

Doses	Parameter	Estimated slope for ln(dose)	Standard error	90% CI	
				Lower	Upper
6.25, 12.5, 25, and 50 mcg	AUC_{0-t}	1.1058	0.0454	1.030	1.182
	C_{max}	1.0855	0.0424	1.015	1.156
6.25, 12.5, and 25 mcg	AUC_{0-t}	1.0716	0.0789	0.940	1.203
	C_{max}	1.0610	0.0680	0.947	1.175

Source: FSS-AS-201, Listing 16.2.6.02 and Listing 16.2.6.03.

AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; CI=confidence interval; C_{max}=maximum observed plasma concentration; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler.

Note: The power model, ln (parameter) = a + b×ln (dose) + error, was used to estimate the slope and corresponding 90% confidence interval.

Note: Actual time for AUC_{0-t} was 0 to 12 hours.

Over the whole dose range of FS MDPI 100/**6.25** to 100/**50** mcg, the increases in salmeterol AUC_{0-t} and C_{max} were slightly greater than dose proportional. For the proposed strength of FS MDPI 100/**12.5** and the bracketing strengths of FS MDPI 100/6.25 and 100/25 mcg, PK parameters for salmeterol increased in an approximately dose proportional manner, as indicated by 90% CI of the slopes that contain unity.

In addition, this was consistent with the *in vitro* proportionality of the delivered and aerodynamic performance between the 3 strengths, FS MDPI 100/6.25, 100/12.5, and 100/50.

Formulation

The clinical development of FS MDPI was originally intended for the US market; therefore, the comparator product used in the clinical studies was the US combination product Advair Diskus. The applicant considered that Advair Diskus and the EU equivalent product (Seretide Accuhaler) can be considered to be clinically the same based on their comparability. The fixed-dose combination FS MDPI was formulated to achieve similar efficacy to Advair Diskus (Seretide Accuhaler), but with a lower nominal dose. This was thought that it was accomplished via improvement in the percentage of inhalable drug particles.

The Applicant was requested by CHMP to further justify the selected dose for salmeterol in FS MDPI. This is presented below.

The formulation development for FS MDPI resulted in a higher amount of salmeterol fine particles fractions compared to salmeterol delivered from Advair Diskus.

The overall systemic exposure (area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration [AUC0-t] ratio) and peak plasma concentration (maximum observed plasma drug concentration [Cmax] ratio) of salmeterol with FS MDPI is approximately 50% and 80%, respectively, that of Advair Diskus. Therefore, the dose selected for further clinical development, based on efficacy in the Phase 2 dose-ranging study, was **12.5 mcg**. Relative to Advair Diskus, the systemic exposure ratio was 0.427 for the AUC0-t and 0.795 for the Cmax (Table 8 and Table 9). The final Phase 3 formulation was assessed in the Phase 1 crossover Study **FSS-AS-10042**, which showed that relative to Advair Diskus the systemic exposure ratio of salmeterol was 0.496 for the AUC0-t and 0.811 for the Cmax.

Table 8: Treatment Comparison of Pharmacokinetic Parameters for Salmeterol (Pharmacokinetic Analysis Set, Study FSS-AS-10042)

Parameter	Treatment	n	Geometric LS mean	GMR	90% CI
C_{max} (pg/mL)	FS MDPI 200/12.5 mcg	35	56.50	0.811	0.70, 0.94
	ADVAIR DISKUS 500/50 mcg	35	69.71		
AUC_{0-t} (pg•h/mL)	FS MDPI 200/12.5 mcg	35	119.65	0.496	0.46, 0.54
	ADVAIR DISKUS 500/50 mcg	35	241.22		
$AUC_{0-\infty}$ (pg•h/mL)	FS MDPI 200/12.5 mcg	34	134.37	0.511	0.47, 0.55
	ADVAIR DISKUS 500/50 mcg	34	262.69		

Source: Study FSS-AS-10042 CSR, Table 18.

$AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; CI=confidence interval; C_{max}=maximum observed plasma drug concentration; CSR=clinical study report; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler; GMR=geometric mean ratio; LS=least squares.

Note: Actual time for AUC_{0-t} was 0 to 36 hours.

Table 9: Treatment Comparison of Pharmacokinetic Parameters for Salmeterol Between FS MDPI Dose Groups and ADVAIR DISKUS 100/50 mcg (Pharmacokinetic Analysis Set, Study FSS-AS-201)

Parameter	n	GMR	90% CI
AUC_{0-t} (pg•h/mL)			
FS MDPI 100/50 mcg vs ADVAIR DISKUS	58	1.929	1.690, 2.202
FS MDPI 100/25 mcg vs ADVAIR DISKUS	59	0.800	0.702, 0.911
FS MDPI 100/12.5 mcg vs ADVAIR DISKUS	**61**	**0.427**	**0.376, 0.485**
FS MDPI 100/6.25 mcg vs ADVAIR DISKUS	59	0.172	0.151, 0.196
C_{max} (pg/mL)			
FS MDPI 100/50 mcg vs ADVAIR DISKUS	58	3.622	3.149, 4.168
FS MDPI 100/25 mcg vs ADVAIR DISKUS	59	1.534	1.335, 1.763
FS MDPI 100/12.5 mcg vs ADVAIR DISKUS	**61**	**0.795**	**0.694, 0.911**
FS MDPI 100/6.25 mcg vs ADVAIR DISKUS	59	0.339	0.295, 0.390

Source: Study FSS-AS-201 CSR, Table 19.

AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; CI=confidence interval; C_{max}=maximum observed plasma drug concentration; CSR=clinical study report; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler; GMR=geometric mean ratio; vs=versus.

Note: Actual time for AUC_{0-t} was 0 to 12 hours.

The AUC0-t represents the systemic exposure due to the drug absorbed by the lungs as well as any absorption of swallowed drug. For drugs that are rapidly absorbed via the lungs, like salmeterol, partial exposure data ($AUC_{0-30min}$) can provide a good estimate of lung delivery because this represents exposure before orally absorbed drug reaches the systemic circulation. As advised in the CHMP Scientific Advice received (EMEA/H/SA/3754/1/2018/II), a post-hoc analysis of salmeterol 30 minutes exposure following administration with FS MDPI was compared to Advair Diskus. This post-hoc analysis of the partial AUC0- 30min and maximum observed plasma drug concentration in the first 30 minutes after administration (Cmax, 0-30min) for salmeterol in Study **FSS-AS-10042** is included in Table 10. Specifically, FS MDPI 200/12.5 mcg was compared to Advair Diskus 500/50 mcg and resulted in ratios of exposure for salmeterol Cmax, 0-30min and AUC0-30min of 0.843 and 0.766, respectively.

Table 10: Treatment Comparison of Post-hoc Pharmacokinetic Parameters for Salmeterol (Pharmacokinetic Analysis Set, Study FSS-AS-10042)

Parameter	Treatment	n	Geometric LS mean	Geometric LS mean ratio	90% CI
$C_{max, 0-30min}$ (pg/mL)	FS MDPI 200/12.5 mcg	35	56.26	0.843	0.72, 0.98
	ADVAIR 500/50 mcg	35	66.72		
$AUC_{0-30min}$ (pg•h/mL)	FS MDPI 200/12.5 mcg	35	16.36	0.766	0.69, 0.85
	ADVAIR 500/50 mcg	35	21.35		

Source: FSS-AS-10042 MAA Adhoc 1.

ANOVA=analysis of variance; $AUC_{0-30min}$=area under the plasma concentration-time curve from time 0 to 30 minutes postdose; CI=confidence interval; $C_{max, 0-30min}$=maximum observed plasma drug concentration in the first 30 minutes after administration; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler; LS=least squares.

Note: An ANOVA model was fitted on the natural logarithm transformation of the pharmacokinetic parameters with sequence, period, and treatment as fixed effects and patient within sequence as a random effect.

Similarly, a post-hoc analysis of the partial area under the plasma concentration-time curve (AUC) and Cmax for salmeterol in Study **FSS-AS-201** is presented in table 26 below. The treatment comparison of FS MDPI 100/12.5 mcg to Advair Diskus 100/50 mcg for salmeterol resulted in ratios for Cmax, 0-30min and AUC0-30min of 0.925 and 0.848, respectively. The Applicant considered that the results indicated that the early exposure due to lung absorption is close to similar for the 2 products and well

within the range where comparable clinical efficacy could be expected. However, the strengths of these products are different.

Furthermore, for orally inhaled drugs such as salmeterol, the overall systemic exposure results from both absorption at the site of action, the lungs, and orally absorbed drug that was swallowed, therefore the overall systemic exposure can be considered as a surrogate indicator for safety. In the applicant's views, the fact that the overall systemic exposure to salmeterol is lower for FS MDPI than for Advair Diskus suggests a more favourable safety profile for FS MDPI (this is further discussed in section 2.6.1 'Discussion on clinical safety').

Specifically, when the comparison of the overall systemic exposure (AUC0-t) and the partial exposure (AUC0-30min) for salmeterol delivered by the 2 inhalers in 2 separate studies are considered side-by-side, FS MDPI is delivered more efficiently to the lungs (AUC0-30min ratios of 0.766 to 0.848) compared to Advair Diskus, while providing an overall systemic exposure ratio that is lower (AUC0-t ratios of 0.427 to 0.496) compared to Advair Diskus (Table 11).

Table 11: Comparison of Salmeterol Total Systemic Exposure and Partial Exposure with the FS MDPI Compared to ADVAIR DISKUS (Pharmacokinetic Analysis Set, Studies FSS-AS-10042 and FSS-AS-201)

Parameter	Ratio of overall exposure FS MDPI vs ADVAIR DISKUS Safety	Ratio of partial exposure FS MDPI vs ADVAIR DISKUS Efficacy
Study FSS-AS-10042	**FS MDPI 200/12.5 mcg vs ADVAIR DISKUS 500/50 mcg**	
AUC (pg•h/mL) GMR	AUC_{0-t} 0.496	$AUC_{0-30min}$ 0.766
C_{max} (pg/mL) GMR	C_{max} 0.811	$C_{max,\ 0-30min}$ 0.843
Study FSS-AS-201	**FS MDPI 100/12.5 mcg vs ADVAIR DISKUS 100/50 mcg**	
AUC (pg•h/mL) GMR	AUC_{0-t} 0.427	$AUC_{0-30min}$ 0.848
C_{max} (pg/mL) GMR	C_{max} 0.795	$C_{max,\ 0-30min}$ 0.925

Source: Table 22, Table 23, Table 24, Table 25.

AUC=area under the plasma concentration-time curve; $AUC_{0-30min}$=area under the plasma concentration-time curve from time 0 to 30 minutes postdose; AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last measurable drug concentration; C_{max}=maximum observed plasma drug concentration; $C_{max,\ 0-30min}$=maximum observed plasma drug concentration in the first 30 minutes after administration; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler; GMR=geometric mean ratio; vs=versus.

The efficacy of different doses of salmeterol was investigated in Study FSS-AS-201 (presented in section 2.5.1 'Dose response studies' and discussed under section 2.5.3 'Discussion on clinical efficacy'). The comparison of the 4 strengths of salmeterol in FS MDPI compared to Advair Diskus showed that the 12.5-mcg strength of salmeterol in FS MDPI (100/12.5 mcg) best matched Advair Diskus 100/50mcg. Thus, the 12.5-mcg dose of FS MDPI (100/12.5 mcg) was selected based on the "matched efficacy" relative to Advair Diskus.

Absorption, Distribution, Metabolism, Elimination

No additional studies have been performed with FS MDPI.

The absorption, distribution, metabolism, and excretion of inhaled Fp and salmeterol delivered in combination have been well described for Advair Diskus and Seretide Accuhaler.

The mean C_{max} of Fp was approximately 62 pg/mL at nominal 200 mcg delivered from the FS MDPI in Study FSS-AS-10042 with a t_{max} of approximately 1 to 2 hours.

The mean C_{max} of salmeterol ranged from 16 to 155 pg/mL at the lowest and highest nominal doses (6.25 and 50 mcg, respectively) in Study FSS-AS-201 and was approximately 60 pg/mL at 12.5 mcg (nominal dose) in Study FSS-AS-10042. The t_{max} for salmeterol was generally 0.1 to 2 hours across both studies.

The rate of absorption of Fp and salmeterol from FS MDPI could be compared to that from Advair Diskus, and both result in low concentrations of circulating Fp and salmeterol after inhalation of recommended doses.

After intravenous administration, the initial disposition phase for Fp was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg. The percentage of Fp bound to human plasma proteins averaged 99%. The percentage of salmeterol bound to human plasma proteins averaged 96% *in vitro*, at concentrations that are much higher than those achieved after administration of therapeutic doses of salmeterol.

Fluticasone propionate has one circulating metabolite, the 17β-carboxylic acid derivative of Fp, which is formed through the cytochrome P450 (CYP) 3A4 pathway. This metabolite has much lower affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor and had negligible pharmacological activity in animal studies. Salmeterol base is extensively metabolised by hydroxylation to α-hydroxysalmeterol (aliphatic oxidation) by CYP3A4.

The total clearance of Fp is high (average, 1093 mL/min), with poly-exponential kinetics. Less than 5% of a radiolabelled oral dose was excreted in the urine as metabolites; the remainder was excreted in the faeces as parent drug and metabolites. Salmeterol elimination is predominantly as α-hydroxysalmeterol in the faeces.

Special populations

In Study **FSS-AS-10042,** subgroup PK analyses by age group (12 to 17 years or ⩾18 years) and by sex were performed. Although the subgroups were small, systemic exposure of Fp and salmeterol for all subgroups in all treatments was not markedly different from the overall study population. The t½ was not impacted by age or sex.

In addition, a population PK analysis was performed for Fp and salmeterol using data from 9 controlled clinical studies that included 350 patients with asthma aged 4 to 77 years who received treatment with the comparator drug Advair Diskus, Advair HFA, Flovent Diskus, Flovent HFA, or chlorofluorocarbon-propelled Fp inhalation aerosol. These analyses showed no clinically relevant effects of age, sex, race, body weight, body mass index, or percent of predicted FEV_1 on apparent clearance and apparent volume of distribution for either Fp or salmeterol.

The effect of hepatic or renal dysfunction on the PK of Fp or salmeterol after administration from FS MDPI has not been studied. However, the applicant confirmed that there was no need to adjust the dose in patients with hepatic or renal impairment.

Pharmacokinetic interaction studies

In Study **FSS-AS-10042**, the exposure of Fp was similar with and without co-administration of salmeterol in the MDPI device (Fp MDPI 200 mcg vs FS MDPI 200/12.5 mcg). This is consistent with the finding that the *in vitro* performance of Fp, evaluated as delivered dose and fine particle dose, is equivalent when comparing the corresponding strengths of the mono and combination therapies.

No studies have been performed with FS MDPI to investigate the effect of Fp on salmeterol PK when given in combination. However, a study comparing salmeterol PK after administration of salmeterol 100 mcg to salmeterol 100 mcg/Fp 500 mcg found that, although salmeterol plasma concentrations were measurable only during the first 0.5 hours after dosing, co-administration of Fp did not affect the Cmax of salmeterol.

The population PK analysis from 9 controlled clinical studies in 350 patients with asthma showed no significant effects on Fp or salmeterol PK after co-administration with beta2-agonists, corticosteroids, antihistamines, or theophyllines.

No studies have been performed with FS MDPI to investigate the potential for drug-drug interactions with other products. However, Fp PK have been studied in drug interaction studies with ritonavir, ketoconazole, and erythromycin and salmeterol PK have been studied in drug interaction studies with ketoconazole and erythromycin (Seretide Accuhaler SmPC).

Because Fp and salmeterol are substrates of CYP3A4, strong CYP3A4 inhibitors have the potential to increase the plasma exposure of Fp (eg, ritonavir and ketoconazole) and salmeterol (eg, ketoconazole and erythromycin) (Seretide Accuhaler). The increased plasma Fp exposure associated with co-administration with ritonavir and ketoconazole also resulted in reduction in serum cortisol area under the plasma concentration-time curve.

2.4.3. Pharmacodynamics

No studies with a PD component were conducted as part of the FS MDPI programme.

In the Phase 3 long-term safety study (FSS-AS-305) using FS MDPI, 24-hour urinary cortisol was collected at baseline, at week 14, and at week 26 to study the effects of medium and high doses of Fp and FS MDPI on the hypothalamic-pituitary-adrenal (HPA) axis. No significant differences across treatments were observed in 24-hour urinary cortisol excretion in patients 12 years of age and older with persistent asthma. Studies for Advair Diskus (see USPI 2019) were conducted with healthy adult subjects and in adult and adolescent patients aged 12 years and older with asthma to examine PD effects of Fp and salmeterol at therapeutic and higher doses. No significant differences were observed in any of the PD effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as Advair Diskus, concurrently with Fp from separate inhalers, or as salmeterol alone. Thus, the systemic PD effects of salmeterol were not altered by the presence of Fp in Advair Diskus. Additionally, no significant differences across treatments were observed by salmeterol on the effects of Fp on the HPA axis (cortisol excretion and plasma cortisol level) (Seretide Accuhaler). No controlled study data with continuous 24-hour electrocardiogram (ECG) monitoring was collected using FS MDPI.

The proposed SmPC (Section 4.5) provides information regarding the potential interactions, based on approved products containing one or more of these components.

2.4.4. Discussion on clinical pharmacology

The objective of the clinical pharmacology programme was to identify (low, mid and high) doses of Fp and salmeterol that could be comparable in efficacy but with lower systemic exposure than the marketed comparators Flovent Diskus and Advair Diskus. This rationale was based on the fact that most of the clinical benefit of ICS is achieved with low-dose ICS along with the fact that the ICS dose-response curve is flat with little increase in efficacy with 2-fold increases in the dose. This suggested that there was room to reduce the ICS dose and corresponding exposure without loss of clinical efficacy, thus, providing benefit to patients. Indirect evidence was used to support the fact that the

doses of Fp and salmeterol demonstrated efficacy comparable to that of Flovent Diskus and Advair Diskus in Phase 2 studies.

Pharmacokinetics

Common methods for the PK analysis were used and were considered appropriate by CHMP. The standard PK parameters were investigated.

No BE studies were performed by the applicant. A formal comparative bioavailability study between FS MDPI and Advair Diskus and/or a formal BE study between FS MDPI and Fp MDPI could have provided more useful information. However, as a full clinical programme was conduction by the applicant, this issue was not further pursued.

Overall, dose proportionality of FS MDPI with respect to the PK parameters has been shown. However, the proposed doses contain significantly lower amounts of the active substances compared to the extensively studied and already marketed combination of Fp and salmeterol. Therefore, the applicant was requested by CHMP to justify the amount of salmeterol, which is considered very low compared to the amount in the already marketed products, with established efficacy/safety and with at least 20 years post-marketing experience. In addition, the results for the AUC0-t for salmeterol were not of the same magnitude as those for the Cmax. AUC0-t for salmeterol is significantly lower, ~46% of the AUC0-t from Advair Diskus50/500mcg, when Cmax is ~74% of the Cmax from Advair Diskus. The Applicant clarified that the formulation of BroPair Spiromax (FS MDPI) was developed to achieve comparable efficacy to the ICS/LABA combination Advair Diskus (Seretide Accuhaler) and, importantly, to achieve this efficacy with a lower nominal dose. The applicant considered that the PK demonstrated that the overall systemic exposure was lower with FS MDPI compared to Advair Diskus, supporting the safety of FS MDPI. Furthermore, the use of 30-minute partial exposure data has been recognised as a mean to assess the efficacy of medicinal products, such as salmeterol, that are characterised by very rapid lung absorption and significant but delayed gastrointestinal absorption. Using this approach, the early exposure (AUC0-30min ratio) in the clinical studies comparing FS MDPI and Advair Diskus resulted in exposure ratios of 0.766 and 0.848, which could support that delivery to the lungs is not substantially less. This was acknowledged by CHMP. However, dose responses for both salmeterol and fluticasone are further discussed in section 2.5.3 'Discussion on clinical efficacy'.

Based on an overall systemic exposure to salmeterol that is lower for FS MDPI than for Advair Diskus, a more favourable safety profile for FS MDPI is suggested by the applicant. However, this is further discussed in the clinical safety section 2.6.1.).

The absorption, distribution, metabolism, and excretion of inhaled Fp and salmeterol delivered in combination have been well described for the authorised Advair Diskus (US). Therefore, much of the data for these sections are referenced from the applicable prescribing information, with FS MDPI data included where applicable. This was considered acceptable by CHMP.

The popPK analysis performed for Fp and salmeterol from comparators showed no clinically relevant effects of age, sex, race, body weight, body mass index, or percent of predicted FEV_1 on apparent clearance and apparent volume of distribution for either Fp or salmeterol. In addition, in study FSS-AS-10042, the PK of FS MDPI appears similar between adolescents and adults. BroPair is indicated for adolescents 12 years and older. No dosage adjustment is considered necessary. There is no need to adjust the dose in elderly patients or in patients with renal impairment. In addition, the effect of hepatic dysfunction on the PK of Fp or salmeterol after administration from FS MDPI has not been studied. This information have been adequately reflected in the SmPC, section 4.2.

Pharmacodynamics

The mechanism of action and the pharmacodynamic properties of both active substances have been studied and are well known from already approved products containing the same active substances and marketed for approximately 20 years. Therefore, no PD studies were conducted as part of the FS MDPI programme, which is acceptable by CHMP. The proposed SmPC provides adequate information regarding potential interactions.

2.4.5. Conclusions on clinical pharmacology

Overall, the PK and PD of fluticasone propionate and salmeterol xinafoate with FS MDPI have been sufficiently characterised to support its approval for the treatment of asthma.

2.5. Clinical efficacy

A full clinical development programme for FS MDPI, including Phase 1 to Phase 3 studies and 2 replicate pivotal Phase 3 efficacy and safety studies was conducted. A monotherapy of Fp MDPI, was included in many of the studies and is mentioned in this report, but the Fp MDPI monotherapy product is not part of this submission.

The clinical development was originally intended for the US market; therefore, the comparator product used in the clinical studies was the US combination product Advair Diskus.

Advair Diskus and the EU equivalent product (Seretide Accuhaler) can be considered to be clinically the same based on their comparability. The 2 inhalers use the same device and the same active ingredient combination of Fp and salmeterol in 12.5 mg lactose monohydrate. While the pre-dispensed (metered) dose strengths for Seretide Accuhaler and Advair Diskus are the same (100/50, 250/50, and 500/50 mcg), there are minor differences in the delivered dose, which would not be expected to impact efficacy or safety.

Furthermore, *in vitro* data demonstrating the comparability of Seretide Accuhaler to Advair Diskus were included in this application in line with the advice received from CHMP (EMEA/H/SA/3754/1/2018/II). The *in vitro* profile of an Advair Diskus batch used in the clinical study (**FSS-AS-305**) fell within the profile for marketed batches of Seretide Accuhaler, indicating that it was a good representative for Seretide Accuhaler. In addition, the PK characteristics described in the respective labels for Seretide Accuhaler and Advair Diskus were reviewed.

2.5.1. Dose response studies

The salmeterol dose used in the Phase 3 clinical programme was chosen based on the efficacy results from a Phase 2 dose-finding study (**Study FSS-AS-201**) and the Fp doses used in the Phase 3 clinical programme were based on the efficacy results from 2 Phase 2 dose-ranging studies (**FpS-AS-201** and **FpS-AS-202**).

2.5.1.1. Study FSS-AS-201

This was a six-period crossover, dose-ranging study to evaluate the efficacy and safety of four doses of FS Spiromax (Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder) administered as single doses compared with single doses of fluticasone propionate Spiromax and open label Advair Diskus in adult and adolescent subjects with persistent asthma.

The primary objective of the study was to evaluate the dose response, efficacy, and safety of 4 different doses of salmeterol (6.25, 12.5, 25, and 50 mcg) each combined with a fixed dose of Fp (100

mcg) delivered as FS MDPI when administered as a single dose in patients 12 years of age and older with persistent asthma. The primary efficacy endpoint was the baseline-adjusted area under the curve for the forced expiratory volume in 1 second (FEV_1) over 12 hours post dose (FEV_1 AUC_{0-12}).

This was a Phase 2, multicentre, randomised, double-blind and open-label, active-controlled, single-dose, 6-period crossover, dose-ranging study. After screening, eligible patients participated in a 14-day run-in period, during which, patients discontinued their asthma medication and were provided with Fp MDPI 50 mcg. Patients were instructed to administer 2 inhalations of Fp MDPI 50 mcg bid. Patients were randomly assigned to 1 of 6 treatment sequences containing the following 6 treatment groups: Treatment A: FS MDPI 100/6.25 mcg, 1 inhalation bid; Treatment B: FS MDPI 100/12.5 mcg 1 inhalation bid; Treatment C: FS MDPI 100/25 mcg, 1 inhalation bid; Treatment D: FS MDPI 100/50 mcg, 1 inhalation bid; Treatment E: Fp MDPI 100 mcg, 1 inhalation bid; Treatment F: Advair Diskus 100/50 mcg, 1 inhalation bid.

All treatments were double-blind, with the exception of Advair Diskus 100/50 mcg, which was open-label. All patients were to participate in all 6 treatment periods and receive all 6 treatments. The 6 treatments were separated by a washout period of 5 to 7 days.

PK results for study FSS-AS-201 are presented in section 2.4.2 'Pharmacokinetics'.

Safety results are presented and discussed in section 2.6 'Clinical safety.'

Efficacy results

For the primary efficacy endpoint of baseline-adjusted FEV1 AUC0-12h, all formulations of FS MDPI were superior ($p<0.0001$) compared with Fp MDPI 100 mcg, indicating that the addition of salmeterol to the Fp formulation improved lung function in patients with asthma. Increases in FEV1 AUC0-12h ranged from 151.7 mL for FS MDPI 100/6.25 mcg to 251.3 mL for FS MDPI 100/50 mcg. The mean increase after Advair Diskus 100/50 mcg (241.9 mL) was similar to that seen after FS MDPI 100/12.5 mcg (252.5 mL) and was also superior ($p<0.0001$) compared to the Fp MDPI 100 mcg formulation without salmeterol.

The baseline-adjusted FEV1 AUC0-12h overall result (FAS) for FS MDPI 100/12.5 mcg was comparable to that for Advair Diskus 100/50 mcg (least squares [LS] mean 3.42 mL; $p=0.8503$). The FEV1 AUC0-12h for the FS MDPI combination with a lower strength of salmeterol (100/6.25 mcg) was significantly lower than that for Advair Diskus (LS mean -41.7 mL; $p<0.0229$). Overall, there was a linear increasing trend in mean values with increasing doses of salmeterol. In the per-protocol analysis set, only FS MDPI 100/50 mcg was significantly superior to Advair Diskus (LS mean 60.29 mL, $p=0.0011$).

While some differences were observed between treatment groups within some cohorts on some efficacy parameters, there was no trend in favour of or against any single treatment, and overall results provided support for the sustained efficacy of FS MDPI as measured by lung function and other important asthma functional endpoints. The demonstration of comparable efficacy results provides further evidence that the small differences in incidence of exacerbations in some of the MDPI groups were due to chance and not due to less efficacy of the MDPI treatment groups relative to the active control.

The Applicant concluded that the clinical data demonstrated a dose response for the range of salmeterol doses tested in the Phase 2 Study FSS-AS-201 that were specifically designed to select the most optimal dose of salmeterol.

2.5.1.2. Study FpS-AS-201

This was a 12-Week dose-ranging study to evaluate the efficacy and safety of Fp Spiromax (Fluticasone Propionate Inhalation Powder) administered twice daily compared with placebo in adolescent and adult subjects with persistent asthma uncontrolled on nonsteroidal therapy.

The primary objective of the study was to evaluate the dose response, efficacy, and safety of 4 different doses of Fp (12.5, 25, 50, and 100 mcg) delivered as Fp MDPI when administered bid in patients 12 years of age and older with persistent asthma who are uncontrolled on nonsteroidal therapy. The primary efficacy endpoint was the change from baseline in trough FEV_1 over the 12-week treatment period.

This was a Phase 2, randomised, double-blind, placebo- and open-label active-controlled, parallel-group, multicentre, dose-ranging study. The study consisted of a 14-day (±2 days) pre-treatment run-in period, during which time, patients continued on their current asthma medications (i.e., non-corticosteroid maintenance medication and short-acting beta 2 agonists [SABAs]). Patients were also instructed to administer 1 inhalation of placebo MDPI (single-blind) bid.

Upon successful completion of the run-in period, patients who continued to meet eligibility criteria were randomly assigned to 1 of 6 treatment groups: Fp MDPI 12.5 mcg, 1 inhalation bid (25 mcg daily dose); Fp MDPI 25 mcg, 1 inhalation bid (50 mcg daily dose); Fp MDPI 50 mcg, 1 inhalation bid (100 mcg daily dose); Fp MDPI 100 mcg, 1 inhalation bid (200 mcg daily dose); Placebo MDPI, 1 inhalation bid; Flovent Diskus 100 mcg, 1 inhalation bid (200 mcg daily dose).

All treatments were double-blind, with the exception of Flovent Diskus 100 mcg, which was open-label. The treatment period lasted for 12 weeks. Plasma pharmacokinetic samples were obtained from a subset of patients before treatment and through 12 hours after administration of the first dose of study drug on day 1.

PK results for study FpS-AS-201 are presented in section 2.4.2 'Pharmacokinetics'.

Safety results are presented and discussed in section 2.6 'Clinical safety.'

<u>Efficacy results</u>

The effect of Fp MDPI was seen on the primary and most secondary measures of asthma control within the first week and maintained over 12 weeks. For the primary efficacy endpoint of trough FEV_1, there was an increase in LS mean FEV_1 from baseline over the 12-week treatment period, with a statistically significantly greater change seen with Fp MDPI 25, 50, and 100 mcg groups when compared with placebo. The change from baseline in trough FEV1 over the 12-week treatment period with Fp MDPI 12.5 mcg was not statistically significantly different from placebo. The magnitude of increases in FEV1 with Fp MDPI suggest a dose response, with greater increases in FEV1 with higher doses of Fp MDPI. Results with Flovent Diskus appeared to be most consistent with the Fp MDPI 25 and 50 mcg groups.

The change from baseline in trough FEV_1 for all Fp MDPI groups was not significantly different when compared with Flovent Diskus.

2.5.1.3. Study FpS-AS-202

This was a 12-week dose-ranging study to evaluate the efficacy and safety of Fp Spiromax (Fluticasone Propionate Inhalation Powder) administered twice daily compared with placebo in adolescent and adult subjects with severe persistent asthma uncontrolled on high dose inhaled corticosteroid therapy.

The primary objective of the study was to evaluate the dose response, efficacy, and safety of 4 different doses of Fp (50, 100, 200, and 400 mcg) delivered as Fp MDPI when administered bid in

patients 12 years of age and older with severe persistent asthma who are uncontrolled on high dose ICS therapy.

The primary efficacy endpoint was the change from baseline in trough FEV_1 over the 12-week treatment period.

This was a Phase 2, randomised, double-blind, placebo- and open-label active-controlled, parallel-group, multicentre, dose-ranging study. The study consisted of a 14-day (±2 days) pre-treatment run-in period, during which, patients continued using their current asthma medications (i.e., SABA and ICS at fixed doses) and were also instructed to administer 1 inhalation of placebo MDPI (single-blind) bid. Upon successful completion of the run-in period, patients who continued to meet eligibility criteria were randomly assigned to 1 of 6 treatment groups: Fp MDPI 50 mcg, 1 inhalation bid (100 mcg daily dose); Fp MDPI 100 mcg, 1 inhalation bid (200 mcg daily dose); Fp MDPI 200 mcg, 1 inhalation bid (400 mcg daily dose); Fp MDPI 400 mcg, 1 inhalation bid (800 mcg daily dose); Placebo MDPI, 1 inhalation bid; Flovent Diskus 250 mcg, 1 inhalation bid (500 mcg daily dose).

All treatments were double-blind, with the exception of Flovent Diskus 250 mcg, which was open-label. The treatment period lasted for 12 weeks. Plasma PK samples were obtained from a subset of patients before treatment and through 12 hours after administration of the first dose of study drug on day 1.

Efficacy results

There was no statistically significant difference in the change in FEV_1 from baseline over the 12-week period between the Fp MDPI dose group and placebo, but there was also no statistically significant difference between Flovent Diskus and placebo, indicating that the study did not have the sensitivity to detect differences in efficacy.

Some differences were seen in favour of Fp MDPI compared with placebo in supportive analyses, particularly in the clinically relevant endpoints of rescue medication use and asthma exacerbations.

The primary efficacy endpoint results showed that no treatment group, including Flovent Diskus, was superior to placebo MDPI in trough FEV1 change from baseline over 12 weeks. Treatment group differences were minimal. Numerically, the results for the Fp MDPI 100 and 200 mcg groups were the most similar to the results for Flovent Diskus (least squares [LS] mean differences from Flovent Diskus of -0.008 and 0.004, respectively). When last observation carried forward (LOCF) approach was used to calculate the trough FEV_1 change from baseline to endpoint, Fp MDPI 200 mcg bid and Flovent Diskus 250 mcg bid were superior to placebo. The improvement in the Fp MDPI 200 mcg bid treatment arm was numerically higher than that in the Flovent Diskus 250 mcg bid treatment arm, but the difference was not statistically significant. As the Fp MDPI 200 mcg bid and Flovent Diskus 250 mcg bid treatment arms were less likely to have patients withdrawn from the study when compared to the placebo MDPI arm, an analysis using an LOCF approach was used to accommodate effects introduced from differential withdrawal rates observed in the study and in recognition that it has been used in other approved development programs such as Flovent Diskus. The secondary efficacy outcomes were similar in that no treatment group was clearly superior to placebo. Over the 12-week treatment period, change in weekly average AM PEF from baseline was not significant for any Fp MDPI dose levels compared with placebo; this was also true for the change in weekly average PM PEF from baseline. The percentage of rescue-free 24-hour periods increased from baseline over the 12-week treatment period for all treatment groups; however, the difference from placebo was not statistically significant for any Fp MDPI group. The probability of remaining in the study (ie, not meeting stopping criteria for worsening asthma) at the end of the 12-week treatment period was significantly higher for all Fp MDPI treatment groups compared with placebo.

PK results for study FpS-AS-202 are presented in section 2.4.2 'Pharmacokinetics'.

Safety results are presented and discussed in section 2.6 'Clinical safety.'

2.5.2. Main studies

To support the efficacy of FS MDPI, 2 replicate, multicentre, placebo-controlled, randomised, parallel-group, 12-week Phase 3 efficacy and safety studies (**FSS-AS- 301** and **FSS-AS-30017**) in adult and adolescent patients (12 years of age or older) with asthma were conducted. In addition to these studies, a 26-week, open-label, long-term safety study with comparator and substitution design was conducted (**Study FSS-AS-305**).

The two replicate phase 3 efficacy and safety studies FSS-AS-301 and FSS-AS-30017 will be presented together, followed by the long-term safety study FSS-AS-305.

Table 12: (Summary of Clinical Efficacy): Description of Phase 3 Clinical Efficacy Studies

Study number	Number of investigational centres Location	Study start Study end Number of patients randomised	Study design	Treatment duration	Dose (twice daily)	Number of patients per group (ITT)	Sex (M/F) Median age years (range)	Primary efficacy endpoints
FSS-AS-301	129 USA, Canada, Poland, Russia, South Africa, Ukraine, Hungary	23 Jul 2014 20 Sep 2015 647	Double-blind, placebo-controlled, randomised, parallel-group	12 weeks	FS MDPI 50/12.5 mcg FS MDPI 100/12.5 mcg Fp MDPI 50 mcg Fp MDPI 100 mcg Placebo	129 129 129 130 130	283/364 43 (12-86)	Change from baseline in trough (morning predose and pre-rescue bronchodilator) FEV_1 at week 12 Standardised baseline-adjusted FEV_1 $AUEC_{0-12h}$ at week 12 (TV9), analysed for the subset of patients who perform postdose serial spirometry
FSS-AS-30017	147 USA, Canada, Czech Republic, Poland, Russia, South Africa, Ukraine, Hungary	01 Oct 2014 26 Sep 2015 728	Double-blind, placebo-controlled, randomised, parallel-group	12 weeks	FS MDPI 100/12.5 mcg FS MDPI 200/12.5 mcg Fp MDPI 100 mcg Fp MDPI 200 mcg Placebo	145 146 146 146 145	289/439 46.5 (12-84)	Change from baseline in trough (morning predose and pre-rescue bronchodilator) FEV_1 at week 12 Standardised baseline-adjusted FEV_1 $AUEC_{0-12h}$ at week 12 (TV9), analysed for the subset patients who perform postdose serial spirometry
FSS-AS-305[a]	103 centres USA	14 Jul 2014 20 Jul 2015 674	Randomised, open-label, active drug-controlled	26 weeks	FS MDPI 100/12.5 mcg FS MDPI 200/12.5 mcg Fp MDPI 100 mcg Fp MDPI 200 mcg FLOVENT HFA 220 mcg FLOVENT HFA 440 mcg ADVAIR DISKUS 250/50 mcg ADVAIR DISKUS 500/50 mcg	120 133 127 126 42 41 41 44	266/406 (2 missing) 40.0-52.0 (median range across groups) (12-79) (overall range)	Change from baseline in trough FEV_1 over the 26-week treatment period[a]

[a] Study FSS-AS-305 was primarily designed to evaluate safety.
F=female; FEV_1=force expiratory volume in 1 second; FEV_1 $AUEC_{0-12h}$=area under the effect curve for forced expiratory volume in 1 second from time 0 to 12 hours postdose; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; ITT=intent-to-treat; M=male; SCE=Summary of Clinical Efficacy; USA=United States of America.

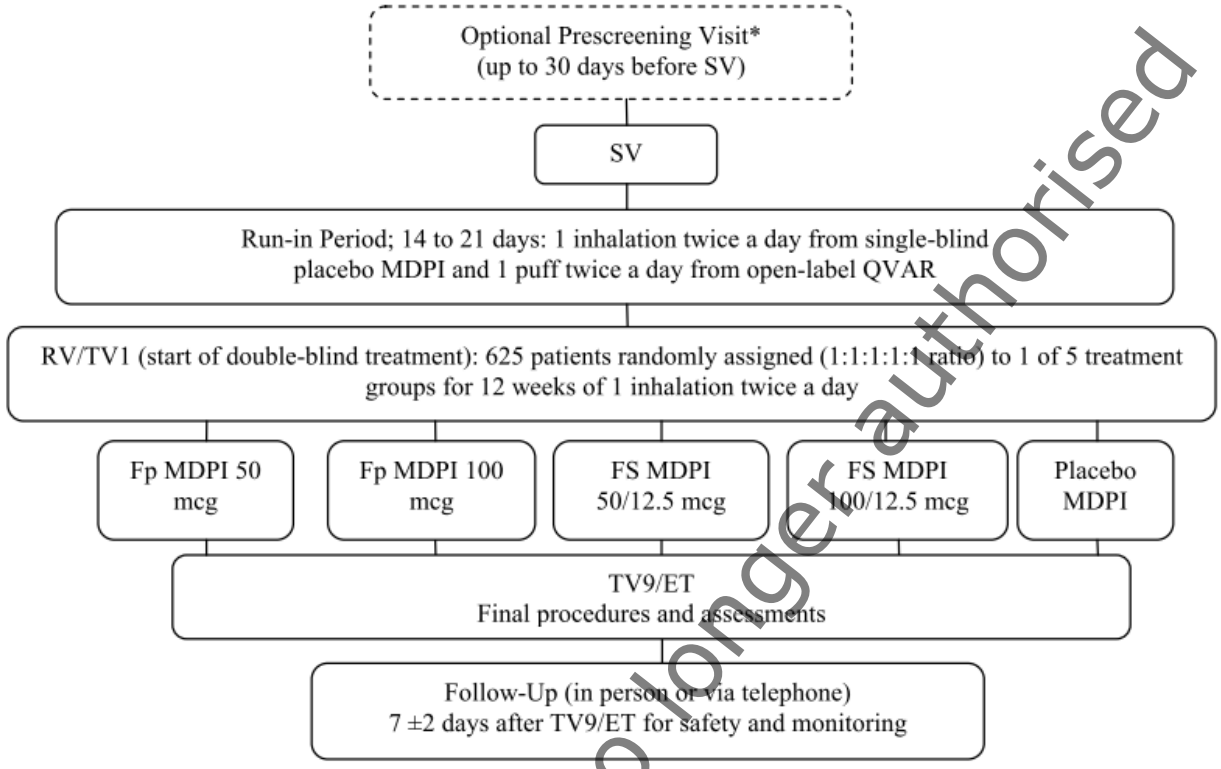
2.5.2.1. Studies FSS-AS-301 and FSS-AS-30017

Title of studies

Study FSS-AS-301: A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone/Salmeterol Multidose

Dry Powder Inhaler in Adolescent and Adult Patients with Persistent Asthma Symptomatic Despite Low-dose or Mid-dose Inhaled Corticosteroid Therapy.

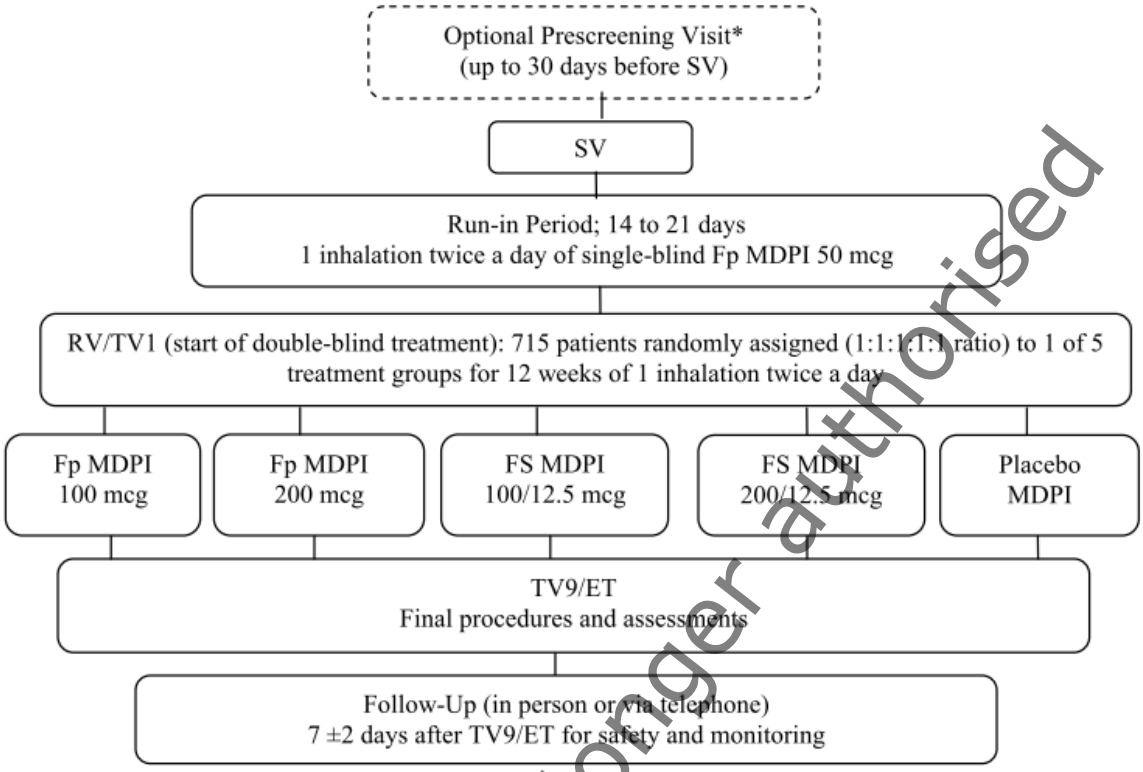
Figure 6: Overall Study FSS-AS-301 Schema



* Required for patients whose prestudy asthma therapy included a LABA in addition to an ICS.
ET = early termination; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; QVAR = beclomethasone dipropionate hydrofluoroalkane metered-dose inhaler; RV = randomization visit; SV = screening visit; TV1 = treatment visit 1; TV9 = treatment visit 9

Study FSS-AS-30017: A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult Patients with Persistent Asthma Symptomatic Despite Inhaled Corticosteroid Therapy.

Figure 7: Overall Study FSS-AS-30017 Schema



* Required for patients whose prestudy asthma therapy included a LABA in addition to an ICS.
ET = early termination; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; RV = randomization visit; SV = screening visit; TV1 = treatment visit 1; TV9 = =treatment visit 9

Methods

Study design

Study FSS-AS-301

A 12-week, multicentre, randomised, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of treatment with 1 inhalation twice a day of Fp MDPI 50 mcg, Fp MDPI 100 mcg, FS MDPI 50/12.5 mcg, or FS MDPI 100/12.5 mcg in adolescents and adults with persistent asthma previously treated with low-dose or mid-dose ICS or ICS/LABA therapy.

Study FSS-AS-30017

A 12-week, multicentre, randomised, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of treatment with 1 inhalation twice a day of Fp MDPI 100 mcg, Fp MDPI 200 mcg, FS MDPI 100/12.5 mcg, or FS MDPI 200/12.5 mcg in adolescents and adults with persistent asthma, previously treated with mid to high dose ICS or ICS/LABA therapy.

Screening

Study FSS-AS-301: Approximately 625 patients (125 per treatment arm) were planned for inclusion in the study. A subset, including approximately 300 patients at selected sites, was planned to perform additional serial spirometry testing at randomisation visit (RV) and week 12. The study consisted of a screening visit (SV), followed by a 14- to 21-day run-in period, a 12-week (±2 days) treatment period, and a 7-day (±2 days) follow-up period, for a total duration of patient participation in this study of

approximately 16 weeks. Patients also had the option to participate in a pre-screening period for up to 30 days.

Study FSS-AS-30017: Approximately 715 patients (143 per treatment arm) were planned for inclusion in the study. A subset, including approximately 300 patients at selected sites, was planned to perform additional serial spirometry testing at RV and week 12. The study consisted of a screening visit (SV) followed by a 14- to 21-day run-in period, a 12-week (±2 days) treatment period, and a 7-day (±2 days) follow-up period, for a total duration of patient participation in this study of approximately 16 weeks. Patients also had the option to participate in a pre-screening period for up to 30 days.

Run-in period (Studies FSS-AS-301 and FSS-AS-30017)

Patients who met all selection criteria at the SV began a 14- to 21-day run-in period. Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI), a SABA inhaler, was provided to replace the patient's current rescue medication, and was to be used as needed for symptomatic relief of asthma symptoms during the run-in and treatment periods.

During the run-in period in the Study **FSS-AS 301**, patients discontinued their current ICS and instead took 1 inhalation twice a day of a single-blinded placebo MDPI device and 1 puff twice a day of an open-label QVAR (beclomethasone dipropionate [a registered trademark of IVAX LLC, a member of the Teva Group]) 40 mcg HFA MDI (or equivalent).

During the run-in period in the Study **FSS-AS -30017**, patients discontinued their current ICS and instead took 1 inhalation twice a day of a single-blinded Fp MDPI 50 mcg.

Patients who failed screening for spirometry or for forced expiratory volume in 1 second (FEV_1) reversibility were permitted to retest once within 7 days of the SV provided that they had met all other selection criteria.

Study Participants (Studies FSS-AS-301 and FSS-AS-30017)

Main Inclusion Criteria

a. **Severity of Disease**: The patient had persistent asthma with a FEV_1 ≥40% and ≤85% of the value predicted for age, height, sex, and race as per the National Health and Nutrition Examination Survey III (NHANES III) reference values at the SV.

b. **Current Asthma Therapy**: Patients were required to have a treatment regimen that included a SABA (albuterol/salbutamol) for use as needed for a minimum of 8 weeks before the SV. Patients were required to have a low-dose or mid-dose of ICS (**Study FSS-AS-301**), a qualifying dose of ICS (**Study FSS-AS-30017**) as part of their asthma management plan, either as ICS monotherapy or as an ICS/LABA combination, for a minimum of 1 month before providing consent.
Patients on ICS/LABA combination therapy were required to have a pre-screening visit in order to change to a comparable dose of ICS monotherapy. The ICS component of the patient's asthma therapy was to be stable for a minimum of 1 month before the ICF was signed.

c. **Reversibility of Disease**: The patient had demonstrated at least 15% reversibility (all patients) and at least a 200-mL increase from baseline FEV_1 (patients age 18 and older) within 30 minutes after 2 to 4 inhalations of albuterol/salbutamol HFA MDI (90-mcg ex-actuator) or equivalent at the SV. Reversibility values of 14.50 to 14.99 were rounded to 15.
Note: Patients who did not qualify for the study due to failure to meet reversibility were permitted to perform a retest once within 7 days or were considered a screen failure and permitted to rescreen once at least 7 days after the date of first screening.

d. **Asthma diagnosis**: The patient had a diagnosis of asthma as defined by the National Institutes of Health (NIH). The asthma diagnosis had been present for a minimum of 3 months and had been stable (defined as no exacerbations and no changes in asthma medication) for at least 30 days before the ICF was signed.

Main Exclusion Criteria

a. The patient had a history of a life-threatening asthma exacerbation that was defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest, or hypoxic seizures.

b. The patient currently smoked or had a smoking history of 10 pack-years or more (a pack-year was defined as smoking 1 pack of cigarettes/day for 1 year). The patient must not have used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco). The patient had a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that had not resolved at least 2 weeks before the SV.

c. The patient had an asthma exacerbation requiring systemic corticosteroids within 30 days before the SV or had any hospitalisation for asthma within 2 months before the SV.

Treatments (Studies FSS-AS-301 and FSS-AS-30017)

Each qualified patient was randomly assigned to 1 of the 5 treatment groups. During the treatment period, each patient received the assigned active or placebo medication. All treatments were administered via Teva MDPI devices with identical external appearance, allowing the double-blind design to be preserved. All treatments were administered as a single inhalation twice a day. All patients were provided with study-specific rescue medication (albuterol/salbutamol HFA MDI) for use on an as-needed basis for the immediate relief of asthma symptoms throughout the treatment period. Study drug was administered twice a day, in the morning (AM) and in the afternoon (PM), after the completion of the asthma symptoms score and the PEF measurements, in that order.

Table 13: Treatment Group Description (Study FSS-AS-301)

Treatment arm	Active devices	Total daily dose	Blinding
A	Fp MDPI 50 mcg	100 mcg	Double-blind
B	Fp MDPI 100 mcg	200 mcg	Double-blind
C	FS MDPI 50/12.5 mcg	100/25 mcg	Double-blind
D	FS MDPI 100/12.5 mcg	200/25 mcg	Double-blind
E	Placebo MDPI	0 mcg	Double-blind

Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler

Table 14: Treatment Group Description (Study FSS-AS-30017)

Treatment arm	Active device	Total daily dose (mcg)	Blinding
A	Fp MDPI 100 mcg	200	Double-blind
B	Fp MDPI 200 mcg	400	Double-blind
C	FS MDPI 100/12.5 mcg	200/25	Double-blind
D	FS MDPI 200/12.5 mcg	400/25	Double-blind
E	Placebo MDPI	0	Double-blind

Objectives (Studies FSS-AS-301 and FSS-AS-30017)

Primary Objective

The primary objective of the studies was to evaluate the efficacy of Fp MDPI and FS MDPI when administered over 12 weeks in patients 12 years of age and older with persistent asthma.

Secondary Objectives

The secondary objectives of the studies were:
-to evaluate the efficacy of Fp MDPI and FS MDPI based on patient-reported outcomes and secondary efficacy measures in patients with persistent asthma treated over 12 weeks;
-to evaluate the safety and tolerability of Fp MDPI and FS MDPI in patients with persistent asthma treated over 12 weeks.

Other Objectives

The other objectives of the studies were to evaluate the efficacy of Fp MDPI and FS MDPI in patients with persistent asthma as assessed by other efficacy measures and patient-reported outcomes.

Outcomes/endpoints (Studies FSS-AS-301 and FSS-AS-30017)

Primary Efficacy Measures and Endpoints

-change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) FEV_1 at week 12 (TV9)

-standardised baseline-adjusted area under the effect curve for forced expiratory volume in 1 second from time zero to 12 hours post-dose (FEV_1 $AUEC_{0\text{-}12h}$) at week 12 (TV9), analysed for the subset of approximately 300 patients who perform post-dose serial spirometry.

Secondary Efficacy Measures and Endpoints

-change from baseline in the weekly average of the daily trough morning PEF over the 12-week treatment period

-change from baseline in the weekly average of the total daily asthma symptom score (the total daily asthma symptom score is the average of the daytime and night time scores) over weeks 1 to 12

-change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12

-time to patient withdrawal for worsening asthma during the 12-week treatment period

-change from baseline in the Asthma Quality of Life Questionnaire with Standardised Activities (AQLQ(S)) (patients ≥18 years of age only) score at week 12 or at endpoint

Important Secondary Endpoints

-time (median and mean) to 15% and 12% improvement from baseline in FEV_1 post-dose at TV1 in the serial spirometry subset

Other Efficacy Measures and Endpoints

-change from baseline in the weekly average of the daily trough evening PEF over the 12-week treatment period

-time to meeting alert criteria for worsening asthma during the 12-week treatment period

-change from baseline in total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over the first 14 days on study drug and change from baseline in the weekly average of total daily (24-hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) at weeks 4, 8, and 12 or at endpoint (ie, the last postbaseline observation)

-change from baseline in the percentage of rescue-free days (defined as 24-hour periods with no rescue medication usage) during the 12-week treatment period

-change from baseline in the percentage of symptom-free days (defined as 24-hour periods with asthma symptom scores of zero) during the 12-week treatment period

-change from baseline in the percentage of asthma-control days (defined as 24-hour periods with asthma symptom scores of zero and no rescue medication usage) during the 12-week treatment period

-proportion of patients meeting alert criteria for worsening asthma during the 12-week treatment period

-proportion of patients withdrawn for worsening asthma during the 12-week treatment period

-change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) FEV1 at weeks 1, 2, 3, 4, 6, 8, 10, and 12 or at endpoint

-change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) forced expiratory flow between 25% and 75% of the forced vital capacity (FEF25-75) over weeks 1 to 12, at weeks 1, 2, 3, 4, 6, 8, 10, and 12 or at endpoint

-change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) forced vital capacity (FVC) over weeks 1 to 12, at weeks 1, 2, 3, 4, 6, 8, 10, and 12 or at endpoint

-proportion of patients who achieve at least 15%, 12%, or 200 mL increase in FEV1 within 12 hours post-dose at TV1 and TV9 or at endpoint

-time (median and mean) to 15% and 12% improvement from baseline in FEV1 post-dose at TV9
-duration of effect: how long patients experience an increase of at least 15% above baseline FEV1 at TV1 and TV9

-proportion of patients achieving a clinically significant change from baseline (minimal important difference [MID] ≥0.5 in the AQLQ(S) [patients ≥ 18 years of age only] or PAQLQ(S) [patients 12 to 17 years of age only]) score at week 12 or at endpoint

-change from baseline in ACT score at weeks 4, 8, and 12, over weeks 1 to 12, or at endpoint

-proportion of patients with ACT score ≤19 at weeks 4, 8, and 12, over weeks 1 to 12, or at endpoint

Simple size

For **Study FSS-AS-301**, sample size and power calculations were mainly driven by demonstrating superiority of Fp MDPI 50 mcg twice daily over placebo in change from baseline in trough FEV_1 at week 12 and the superiority of FS MDPI 50/12.5 mcg twice daily over Fp MDPI 50 mcg twice daily in standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12.

For the superiority comparison of Fp MDPI 50 mcg twice daily versus placebo in **change from baseline in trough FEV_1 at week 12**, assuming that the change from baseline in trough FEV_1 at week 12 is analysed using an analysis of variance (ANOVA) model with only a single factor of treatment group, that a true treatment difference is 130 mL between Fp MDPI 50 mcg twice daily and placebo, and that a common SD is 314 mL, then **106 patients** per treatment group (**a total of 530 patients**) yields an approximate statistical power of 85%, at a significance level of 0.05, for the 2-sided superiority test of Fp MDPI 50 mcg twice daily versus placebo. The treatment effect and variability assumptions made for this power calculation were based on data collected in the applicant's studies.

For the superiority comparison of FS MDPI 50/12.5 mcg twice daily and Fp MDPI 50 mcg twice daily in **standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12** in the serial spirometry subset, assuming that the standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 is analysed using an ANOVA model with only a single factor of treatment group, that a true treatment difference is 200 mL between FS MDPI 50/12.5 mcg twice daily and Fp MDPI 50 mcg twice daily, and that a common SD is 200 mL, then **48 patients** per treatment group (**a total of 240 patients**) yields a statistical power of greater than 99%, at a significance level of 0.05, for the 2-sided superiority test of FS MDPI 50/12.5 mcg twice daily versus Fp MDPI 50 mcg twice daily. The treatment effect and variability assumptions made for this power calculation were based on data collected in previous the applicant's studies.

Assuming a dropout rate of 15%, **125 patients per treatment group** (**a total of 625 patients**, with a subset of approximately 300 patients who performed serial spirometry) yields a statistical power of at least 85%, at a significance level of 0.05, for demonstrating superiority of Fp MDPI 50 mcg twice daily over placebo and superiority of FS MDPI 50/12.5 mcg twice daily over Fp MDPI 50 mcg twice daily.

For **Study FSS-AS-30017**, sample size and power calculations were mainly driven by demonstrating superiority of Fp MDPI 100 mcg twice daily over placebo in change from baseline in trough FEV_1 at week 12 and the superiority of FS MDPI 100/12.5 mcg twice daily over Fp MDPI 100 mcg twice daily in standardised baseline-adjusted FEV_1, $AUEC_{0\text{-}12h}$ at week 12.

For the superiority comparison of Fp MDPI 100 mcg twice daily versus placebo in **change from baseline in trough FEV_1 at week 12**, assuming that the change from baseline in trough FEV_1 at week 12 is analysed using an analysis of variance (ANOVA) model with only a single factor of treatment group, that a true treatment difference is 130 mL between Fp MDPI 100 mcg twice daily and placebo, and that a common SD is 336 mL, then **121 patients** per treatment group (**a total of 605 patients**) yields an approximate statistical power of 85%, at a significance level of 0.05, for the 2-sided superiority test of Fp MDPI 100 mcg twice daily versus placebo. The treatment effect and variability assumptions made for this power calculation are based on data collected in Teva studies.

For the superiority comparison of FS MDPI 100/12.5 mcg twice daily versus Fp MDPI 100 mcg twice daily in **standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12**, assuming that the standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 is analysed using an ANOVA model with only a single factor of treatment group, that a true treatment difference is 200 mL between FS MDPI 100/12.5 mcg twice daily and Fp MDPI 100 mcg twice daily, and that a common SD is 200 mL, then **48 patients** per treatment group (**a total of 240 patients**) yields a statistical power of greater than

99%, at a significance level of 0.05, for the 2-sided superiority test of FS MDPI 100/12.5 mcg twice daily versus Fp MDPI 100 mcg twice daily. The sample size of 300 patients performing serial spirometry assumes a dropout rate of up to approximately 20%. The treatment effect and variability assumptions made for this power calculation are based on data collected in previous Teva studies.

Assuming a dropout rate of 15%, **143 patients per treatment group** (**a total of 715 patients**, with a subset of approximately 300 patients who perform serial spirometry) yields a statistical power of at least 85%, at a significance level of 0.05, for demonstrating superiority of Fp MDPI 100 mcg twice daily over placebo and superiority of FS MDPI 100/12.5 mcg twice daily over Fp MDPI 100 mcg twice daily.

Randomisation and blinding (masking) Studies FS-AS-301 and FSS-AS-30017

Study FSS-AS-301 was a double-blind, parallel-group, placebo-controlled randomised clinical study. Patients who met all randomisation criteria at the RV were randomly assigned to receive Fp MDPI 50 mcg, Fp MDPI 100 mcg, FS MDPI 50/12.5 mcg, FS MDPI 100/12.5 mcg, or placebo MDPI in a 1:1:1:1:1 ratio for the entire 12-week treatment period. Randomisation was assigned using interactive response technology (IRT). Approximately 125 patients were randomised into each treatment arm. After randomisation, patients and investigators remained blinded to randomised treatment assignment during the study. In addition, the sponsor's clinical personnel involved in the study were blinded to the study drug identity after the run-in period until the database was locked for analysis and the treatment assignment was revealed.

Study FSS-AS-30017 was a double-blind, parallel-group, placebo-controlled randomized clinical study. Patients who met all randomisation criteria at the RV were randomly assigned to receive Fp MDPI 100 mcg, Fp MDPI 200 mcg, FS MDPI 100/12.5 mcg, FS MDPI 200/12.5 mcg, or placebo MDPI in a 1:1:1:1:1 ratio for the entire 12-week treatment period. Randomisation was assigned using interactive response technology. Approximately 143 patients were randomised into each treatment arm. After randomisation, patients and investigators remained blinded to randomised treatment assignment during the study. In addition, the sponsor's clinical personnel involved in the study were blinded to the study drug identity after the run-in period until the database was locked for analysis and the treatment assignment was revealed.

Statistical methods (Studies FSS-AS-301 and FSS-AS-30017)

Hypothesis: These were superiority trials. The list of primary and secondary endpoints controlled for Type I error under Multiplicity section is included below.

Primary endpoint and analysis
The primary analysis of trough FEV1 was conducted in FAS, and FEV1 AUECO0-12h in Serial Spirometry Subset, whereas supportive analyses in ITT and PP.

The baseline FEV1 was the average of the 2 pre-dose FEV1 measurements (30 and 10 minutes pre-dose) at the RV. If 1 pre-dose FEV1 measurement was missing, the other non-missing measurement was used as baseline; if both pre-dose FEV1 measurements were missing, baseline was treated as missing. In order to account for missing data, the modified baseline observation carried forward (BOCF) method was implemented.

The analysis of change from baseline in trough FEV1 at week 12 was performed using an ANCOVA model with effects due to baseline trough AM FEV1, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment.

Baseline-adjusted FEV1 was calculated as post-dose FEV1 after subtracting the baseline FEV1 value. If a patient was missing post-dose spirometry measurements intermittently, then those missing values were ignored, and the trapezoidal rule simply spanned the missing timepoint(s).
The analysis of standardised baseline-adjusted FEV1 AUEC0-12h was performed using an ANCOVA model with fixed effects of treatment, sex, (pooled) centre, previous therapy (ICS or ICS/LABA), and with covariates of age and baseline FEV1. For those serial spirometry patients who did not perform serial spirometry at week 12, missing data were imputed via LOCF, which is the last observed serial spirometry, performed either ET (early termination) or TV1 (baseline). A sensitivity analysis used a modified BOCF method, where the post-dose value of FEV1 at TV1 was used.

Sensitivity analyses:

- A cumulative proportion of responders analysis (CPRA) graph (Farrar et al, 2006) was provided for the change from baseline in trough FEV1 at week 12
- Tipping Point Analysis for change from baseline in trough FEV1 at Week 12. This is a sensitivity analysis utilizing multiple imputations under the MNAR assumption.
- Other Multiple Imputation Sensitivity Analysis for Change from Baseline in trough FEV1 at Week 12. Like the tipping point analysis, this analysis described utilizes multiple imputations under the MNAR assumption for those patients who withdrew due to worsening asthma. Missing data for patients who withdrew for other reasons are treated as MAR.
- Sensitivity Analysis for Standardised Baseline-adjusted FEV1 AUEC0-12h at Week 12: For those serial spirometry patients who withdrew due to worsening of asthma, and did not perform serial spirometry at week 12, missing data were to be imputed via BOCF. For patients who withdrew due to other reasons, missing data were to be imputed via LOCF, which is the last observed serial spirometry performed either ET or TV1 will be carried forward.

Analysis sets

The intent-to-treat (ITT) population included all randomised patients. Treatment was assigned based upon the treatment to which patients were randomised regardless of which treatment they received. The ITT population served as the supportive population for efficacy analyses.

The full analysis set (FAS) included all patients in the ITT population who received at least 1 dose of study drug and had at least 1 postbaseline trough FEV1 assessment. The FAS served as the primary analysis set for efficacy analyses. Pulmonary function test data could be excluded from the FAS for visits in which patients took (within 7 days of the visit) any of a limited subset of prohibited asthma medications that could significantly confound interpretation. These medications were oral or systemic corticosteroids; LABAs or long-acting muscarinic antagonists, leukotriene receptor antagonists/5-leukotriene oxidase inhibitors (eg, zileuton [ZYFLO (Cornerstone Therapeutics)]); and oral B-agonists. A blinded statistical data review (SDR) meeting was conducted before database lock in order to determine and document the PFT data excluded from the FAS.

The per-protocol (PP) population included all data from randomised patients prior to experiencing a major protocol violation and who had greater than 80% compliance to the study drug over the entire treatment period. Patient diary data were the primary source for the compliance calculations, unless otherwise specified. Major protocol violations were determined prior to unblinding. Note that since the use of incorrect study drug was considered a major protocol violation, for treatment assignment in the PP population, "as randomised" coincided with "as treated." The PP population served as the supportive population for the primary efficacy analysis only.

The safety population included all randomised patients who received at least 1 dose of study drug. In this population, treatment was assigned based upon the treatment patients actually received regardless of the treatment to which they were randomised. The safety population was used for all analyses of safety data.

Serial Spirometry Subset. A subset of approximately 300 patients who performed post-dose serial spirometry was used for the primary endpoint of the standardised baseline-adjusted FEV1 AUEC0-12h at week 12 and for other postdose spirometry endpoints. These patients were enrolled at investigational centres that were preselected based on their capabilities and prior experience with serial spirometry. If an investigational centre was designated as a serial investigational centre, then all patients at that investigational centre were serial spirometry patients. Patients could not opt out of serial spirometry participation.

Missing data

For the primary endpoint of change from baseline in trough FEV1 at week 12, missing data caused by early dropout from the study were handled by penalizing the positive change from baseline in trough FEV1 score using a baseline observation carried forward (BOCF) method. This method assigned these patients a change from baseline in trough FEV1 score of zero, thus the discontinued patients were treated as failures and were assigned a poor score. Discontinued patients that have negative change from baseline with last non-missing FEV1 score did not have their results adjusted, since their scores was already poor.

For the supporting primary endpoint of standardised baseline-adjusted trough FEV1 AUEC0-12wk, missing data were handled similarly.

For the mixed model for repeated measures (MMRM), there were no imputation for missing data. For the ANCOVA model, except for the primary endpoint change from FEV1 at week 12 and the standardised baseline-adjusted trough FEV1 AUEC0-12wk, missing data were imputed via last observation carried forward (LOCF).

For the tipping point sensitivity analysis, missing FEV1 values were imputed for patients who discontinued treatment before the week 12 visit. Missing FEV1 values in the placebo group are assumed missing at random (MAR). Missing FEV1 values for the active treatment groups were imputed in the same manner, but then a constant (positive value) shift was subtracted from the imputed FEV1 values. The initial shift value was zero (representing MAR) and it then was increased, and the process repeated until the treatment effect is no longer significant at the 5% level. Similar to the tipping point analysis, the other sensitivity analysis described utilizes multiple imputations under the missing not at random (MNAR) assumption for those patients who withdrew due to worsening asthma. Missing data for patients who withdrew for other reasons are treated as MAR.

Multiplicity

FSS-AS-301: A fixed-sequence multiple testing procedure was used to control the overall Type I error rate at the 0.05 level (2-sided) for the primary endpoints analysis. The same testing sequence was used in *FSS-AS-30017*: for Standardised baseline-adjusted FEV1 AUEC0-12h at week 12: 1) FS 200/12.5 vs Fp200, 2)FS 100/12.5 vs Fp 100, 3) FS200/12.5 vs Placebo, 4) FS 100/12.5 vs Placebo; for trough FEV1: 5) FS200/12.5 vs Placebo, 6) FS100/12.5 vs Placebo, 7) Fp200 vs Placebo, 8) Fp100 vs Placebo.

If the p-value was less than 0.05 for all inferential comparisons for the primary analysis, then inferential testing was extended to the secondary analysis.

Results

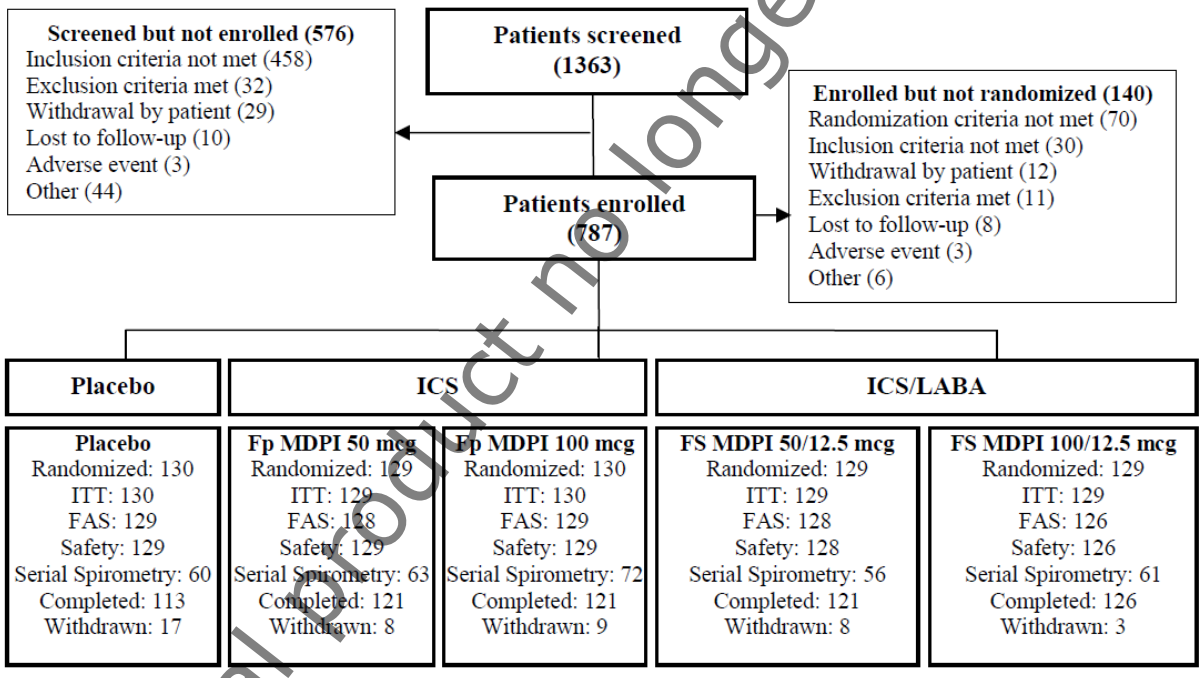
Participant flow

Study FSS-AS-301

647 patients with persistent asthma were randomly assigned to treatment as follows:
-placebo: 130 patients (1 was not treated)
-Fp MDPI 50 mcg: 129 patients
-Fp MDPI 100 mcg: 130 patients (1 was not treated)
-FS MDPI 50 mcg/12.5 mcg: 129 patients (1 was not treated)
-FS MDPI 100 mcg/12.5 mcg: 129 patients (2 were not treated)

These 647 patients were included in the ITT population. A total of 641 (>99%) patients received at least 1 dose of study drug and were evaluable for safety; 640 (99%) patients were included in the FAS, and 602 (93%) completed the study.

Figure 8: Study Participant Flow (Study FSS-AS-301)



Source: Summary 15.1.1, Listing 16.2.1.1, and Listing 16.2.1.2.
ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone/salmeterol multidose dry powder inhaler; ITT = intent-to-treat; FAS = full analysis set

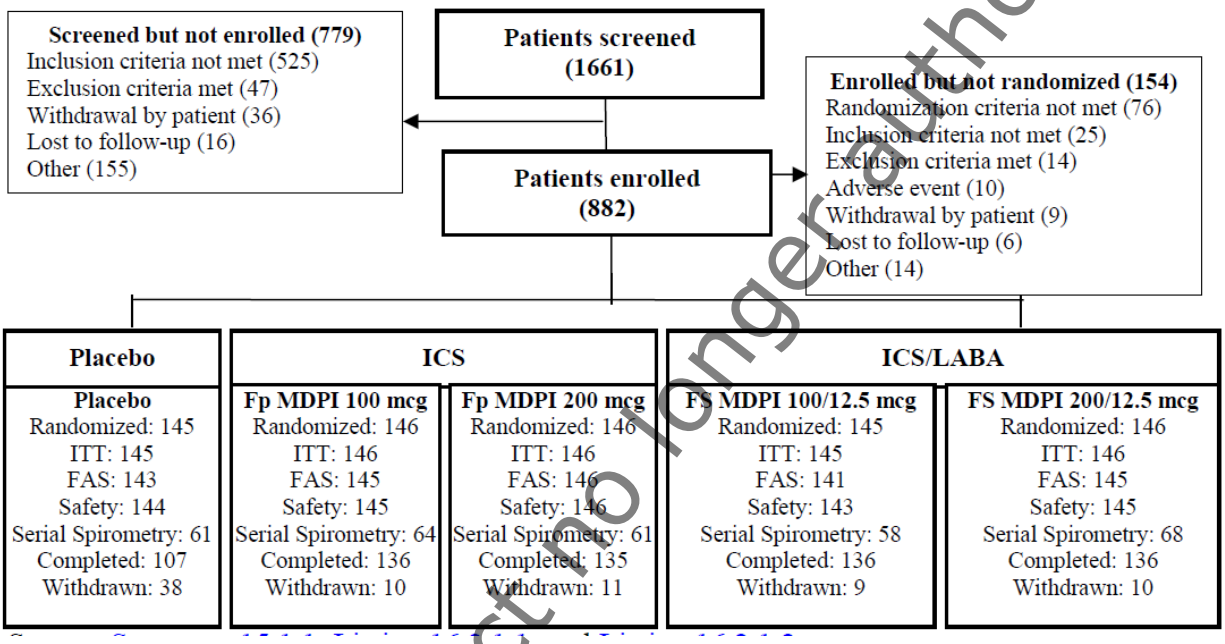
Study FSS-AS-30017

728 patients with persistent asthma were randomly assigned to treatment as follows:
-placebo: 145 patients (1 was not treated)
-Fp MDPI 100 mcg: 146 patients (1 was not treated)
-Fp MDPI 200 mcg: 146 patients
-FS MDPI 100 mcg/12.5 mcg: 145 patients (2 were not treated)
-FS MDPI 200 mcg/12.5 mcg: 146 patients (1 was not treated)
These 728 patients were included in the ITT population. A total of 723 (>99%) patients received at least 1 dose of study drug and were evaluable for safety; 720 (99%) patients were included in the

FAS, and 650 (89%) completed the study, including 107 (74%) patients in the placebo group and ranging from 135 to 136 (92% to 94%) patients in the active treatment groups.

A total of 78 (11%) patients discontinued from the study (38 [26%] receiving placebo, 10 [7%] receiving Fp MDPI 100 mcg, 11 [8%] receiving Fp MDPI 200 mcg, 9 [6%] receiving FS MDPI 100/12.5 mcg, and 10 [7%] receiving FS MDPI 200/12.5 mcg). The most frequent reason for withdrawal was disease progression, which occurred for 24 (3%) patients overall, including 18 (12%) patients in the placebo group. Another 9 (1%) patients discontinued due to lack of efficacy, including 7 (5%) patients in the placebo group.

Figure 9: Study Participant flow (Study FSS-AS-30017)



ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone/salmeterol multidose dry powder inhaler; ITT = intent-to-treat; FAS = full analysis set

Recruitment

Study FSS-AS-301 Period: 23 July 2014 to 21 September 2015

Duration of Treatment: The total duration of patient participation in this study was approximately 16 weeks, which included a run-in period (14 to 21 days); a double-blind treatment period (12 weeks ±2 days); and a follow-up period (7 ±2 days). Patients also had the option to participate in a pre-screening period for up to 30 days before the SV, during which no study drug was administered.

Study FSS-AS-30017 Period: 01 October 2014 to 26 September 2015

Duration of Treatment: The total duration of patient participation in this study was approximately 16 weeks, which included a run-in period (14 to 21 days); a double-blind treatment period (12 weeks ±2 days); and a follow-up period (7 ±2 days). Patients could also participate in an optional pre-screening period for up to 30 days before the SV, during which no study drug was administered.

Conduct of the study

Study FSS-AS-301

The primary reasons for Amendment 03 Dated 14 July 2015 are the changes to the primary endpoint, secondary endpoints, and the sequence of the multiple testing procedures for the secondary endpoints. The changes are based on feedback from regulatory authorities. This revision was considered substantial. Non-substantial revisions have been made to the protocol (and protocol synopsis, as appropriate).

The primary reason for Amendment 02 Dated 19 February 2015 was the change to the inclusion criteria to allow patients on low-dose and mid-dose ICSs to participate in this study which evaluates the efficacy of both low-dose and mid-dose ICS containing study drugs. This revision was considered to be substantial. Other non-substantial revisions were made to the protocol (and protocol synopsis, as appropriate).

The primary reason for Amendment 01 Dated 17 November 2014 was the change to the primary endpoint as requested by FDA on 19 July 2014. This revision was considered to be substantial. Additionally, there was a clarification to when a severe asthma exacerbation would be considered a serious adverse event. Other non-substantial revisions were made to the protocol (and protocol synopsis, as appropriate).

Study FSS-AS-30017

There were 4 global amendments to the protocol for this study and 3 administrative letters. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study at the time of each amendment.

A protocol version specific to Canada (dated 31 July 2014) was needed to satisfy a Health Canada requirement that patients be informed about study drugs given during the run-in period. Therefore, while the global protocol specifies single-blind placebo during the run-in period, the protocol for investigational centres in Canada specifies open-label placebo. Updated versions of the country-specific protocol were issued with subsequent amendments to the global protocol.

Amendment 1 (dated 02 December 2014) to the protocol was issued after 147 patients had been enrolled into the study.

The following major procedural changes (not all-inclusive) were made to the protocol:

- Rescreening and retesting procedures for spirometry and reversibility were clarified.
- Spirometry procedures were updated from 5 to 8 permissible efforts per test.
- Clarification was provided about when a severe asthma exacerbation would be considered a serious adverse event.

Amendment 2 (dated 10 December 2014) to the protocol was issued when 147 patients had been enrolled into the study to correct the EudraCT number on the signature page.

Amendment 3 (dated 19 February 2015) to the protocol was issued when 543 patients had been enrolled into the study.

The following major procedural changes (not all-inclusive) were made to the protocol:

- Inclusion criteria were updated to allow patients who had had changes in their ICS treatment over 1 month prior to screening to participate.

Amendment 4 (dated 09 April 2015) to the protocol was issued when 602 patients had been enrolled into the study.

The following major procedural changes (not all-inclusive) were made to the protocol:

- Based on discussions with the US FDA, the analysis of the primary endpoint of change from baseline in trough FEV_1 was changed from over the 12-week treatment period to at week 12, and the primary endpoint for serial spirometry was specified as standardised baseline-adjusted FEV_1 $AUEC_{0-12h}$ at week 12 (TV9).
- As recommended by the FDA for a similar study, the CPRA graph was added to examine all possible response levels of interest.
- Related to the change in the primary endpoint, the analysis methods were changed, the methods for handling missing data were modified, and the sequential order of comparisons was adjusted.
- Statistical power considerations were recalculated based on the change in the primary endpoint and on newly available data from Teva studies.
- A subgroup analysis by region (US and non-US) was added.

Baseline data

Study FSS-AS-301

The treatment groups were similar with regard to age (mean age ranged from 40.6 to 43.3 years

across groups), sex (slightly over half female in all groups), race (approximately three-quarters white in all groups), and BMI (mean BMI ranged from 27.63 to 28.00 kg/m2 across groups). The FAS was nearly identical to the ITT population in these characteristics. In the serial spirometry subset, which included about half as many patients as the ITT population, mean ages were slightly younger, the proportions of patients who were black were greater, the proportions of patients who were Hispanic or Latino were greater, and mean BMIs were slightly greater relative to the ITT population.

Study FSS-AS-30017

The treatment groups were similar with regard to age (mean age ranged from 44.3 to 45.7 years across groups), sex (approximately 60% female in all groups), race (approximately 80% white in all groups), and BMI (mean BMI ranged from 29.3 to 30.2 kg/m2 across groups). The FAS was nearly identical to the ITT population in these characteristics. In the serial spirometry subset, which included under half as many patients as the ITT population, mean ages were slightly younger, the proportions of patients who were black were greater, and mean BMIs were slightly greater relative to the ITT population.

All patients enrolled in the study were required to have persistent asthma. Baseline spirometry results were generally similar between patients across treatment groups; mean FEV1 ranged from 2.069 L to 2.157. Among the 120 (16%) patients overall who were prior smokers, the proportions did not differ greatly across treatment groups. However, mean numbers of pack-years ranged from 2.9 for FS MDPI 200/12.5 mcg to 4.8 for Fp MDPI 200 mcg. The proportions of patients whose previous asthma therapy included an ICS/LABA ranged from 50% (73 of 146 patients in the FS MDPI 200/12.5 mcg group) to 60% (88 of 146 patients in the Fp MDPI 100 mcg group; Table 19). The FAS was nearly identical to the ITT population in these characteristics.

Table 15: (Summary of Clinical Efficacy): Baseline Disease Characteristics by Treatment Group (Intent-to-Treat Population)

Baseline characteristic	Placebo (N=275)	Fp MDPI (bid)				FS MDPI (bid)				Total (N=1375)
		50 mcg (N=129)	100 mcg (N=276)	200 mcg (N=146)	Combined (N=551)	50/12.5 mcg (N=129)	100/12.5 mcg (N=274)	200/12.5 mcg (N=146)	Combined (N=549)	
FEV_1 (L)										
n	273	129	274	146	549	128	268	145	541	1363
Mean (SD)	2.2 (0.63)	2.1 (0.63)	2.1 (0.59)	2.1 (0.57)	2.1 (0.59)	2.3 (0.65)	2.2 (0.60)	2.1 (0.65)	2.2 (0.63)	2.1 (0.62)
Median	2.1	2.0	2.1	2.0	2.0	2.2	2.1	1.9	2.1	2.1
Min, max	0.8, 3.9	0.8, 4.1	0.9, 4.1	0.9, 3.6	0.8, 4.1	1.0, 3.9	1.1, 4.0	0.8, 3.7	0.8, 4.0	0.8, 4.1
FVC (L)										
n	273	129	274	146	549	128	268	145	541	1363
Mean (SD)	3.2 (0.94)	3.2 (0.97)	3.2 (0.92)	3.2 (0.89)	3.2 (0.93)	3.4 (0.94)	3.3 (0.90)	3.2 (1.00)	3.3 (0.94)	3.2 (0.93)
Median	3.1	3.0	2.9	3.0	3.0	3.2	3.1	3.1	3.1	3.0
Min, max	1.3, 5.9	1.4, 6.1	1.3, 6.5	1.4, 5.5	1.3, 6.5	1.4, 6.3	1.4, 6.6	1.3, 6.7	1.3, 6.7	1.3, 6.7
FEF_{25-75} (L/s)										
n	273	129	274	146	549	128	268	145	541	1363
Mean (SD)	1.4 (0.69)	1.4 (0.60)	1.5 (0.73)	1.3 (0.66)	1.4 (0.68)	1.7 (0.84)	1.4 (0.65)	1.3 (0.70)	1.5 (0.72)	1.4 (0.70)
Median	1.3	1.3	1.3	1.2	1.3	1.7	1.3	1.2	1.3	1.3
Min, max	0.4, 4.1	0.3, 3.4	0.2, 4.2	0.3, 3.7	0.2, 4.2	0.3, 5.2	0.2, 3.6	0.3, 4.7	0.2, 5.2	0.2, 5.2
FEV_1/FVC (%)										
n	273	129	274	146	549	128	268	145	541	1363
Mean (SD)	67.3 (9.84)	67.1 (9.00)	68.1 (10.77)	66.0 (10.85)	67.3 (10.42)	69.1 (11.65)	66.8 (9.89)	65.3 (10.43)	66.9 (10.54)	67.2 (10.35)
Median	67.3	67.2	67.9	65.4	67.4	69.9	67.2	65.0	67.3	67.3

Baseline characteristic	Placebo (N=275)	Fp MDPI (bid)				FS MDPI (bid)				Total (N=1375)
		50 mcg (N=129)	100 mcg (N=276)	200 mcg (N=146)	Combined (N=551)	50/12.5 mcg (N=129)	100/12.5 mcg (N=274)	200/12.5 mcg (N=146)	Combined (N=549)	
Min, max	38.0, 90.3	44.7, 94.6	37.5, 99.5	38.6, 98.5	37.5, 99.5	40.3, 95.8	41.5, 95.4	40.3, 93.2	40.3, 95.8	37.5, 99.5
Percent of predicted FEV_1 (%)										
n	273	129	274	146	549	128	268	145	541	1363
Mean (SD)	66.2 (10.96)	66.5 (9.87)	66.6 (10.24)	64.0 (10.07)	65.9 (10.16)	69.7 (10.87)	66.2 (11.04)	64.7 (11.23)	66.6 (11.18)	66.2 (10.73)
Median	68.5	67.5	67.0	64.8	66.5	72.0	67.5	66.0	68.5	67.5
Min, max	41.0, 84.5	45.0, 84.0	40.5, 85.5	40.5, 85.5	40.5, 85.5	41.0, 85.0	41.0, 92.0	40.0, 85.5	40.0, 92.0	40.0, 92.0
Previous asthma therapy, n (%)										
ICS	170 (62)	89 (69)	141 (51)	63 (43)	293 (53)	90 (70)	164 (60)	73 (50)	327 (60)	790 (57)
ICS/LABA	105 (38)	40 (31)	135 (49)	83 (57)	258 (47)	39 (30)	110 (40)	73 (50)	222 (40)	585 (43)

Source: Module 5.3.5.3, Summary 3.1
bid=twice daily; FEF_{25-75}=forced expiratory flow between 25% and 75% of the forced vital capacity; FEV_1=forced expiratory volume in 1 second; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; FVC=forced vital capacity; ICS=inhaled corticosteroid; LABA=long-acting β_2 agonist; max=maximum; min=minimum; n=number of patients; SD=standard deviation; SE=standard error.

Numbers analysed

Jointly in 2 studies, 1375 patients were randomised to Fp MDPI, FS MDPI, or placebo treatment, and of those patients, 1360 were included in the FAS population. The majority of patients in all treatment groups in the FAS population completed the study.

Only 9% of patients overall discontinued the studies prematurely. The most common reasons for discontinuation overall were withdrawal by subject, disease progression, adverse events, and lack of efficacy.

In both studies, proportionally more patients who received placebo treatment (55 [20%] patients) discontinued from the studies than those who received Fp MDPI or FS MDPI treatment (30 [5%]

patients in the combined FS MDPI group). This disparity is due to discontinuation due to disease progression (3 [<1%] patients in the combined FS MDPI groups), lack of efficacy (1 [<1%] patient in the combined FS MDPI groups), and adverse events (7 [1%] patients in the combined FS MDPI groups), all of which were higher in the placebo group than in the Fp MDPI or FS MDPI groups. The proportion of patients completing or discontinuing the studies were similar in the Fp MDPI and FS MDPI groups.

In both Studies FSS-AS-301 and FSS-AS-30017, the difference in the number of patients was minimal between the FAS and ITT populations, which were used as the primary and supportive populations, respectively, for the efficacy analyses.

In **Study FSS-AS-301**, the ITT population included 647 patients. The FAS included 640 patients, reflecting the exclusion of 7 patients relative to the ITT population, as follows (by definition, patients who were randomised but not treated were included in the ITT population for analysis, but excluded from the FAS population). Of these 7 patients excluded from the FAS (of which one did not meet selection criteria and 6 did not meet randomisation criteria but was randomised in error), only 1 patient was treated with study drug.

In **Study FSS-AS-30017**, the ITT population included 728 patients. The FAS included 720 patients, reflecting the exclusion of 8 patients relative to the ITT population. Of these 8 patients excluded from the FAS (of which 3 did not meet selection criteria and 2 did not meet randomisation criteria and were not treated but were randomised in error, only 3 patients were treated with study drug.

Table 16: (Summary of Clinical Efficacy): Patient Disposition by Treatment Group (All Patients, Studies FSS-AS-301 and FSS-AS-30017 Pooled)

		Fp MDPI (bid)				FS MDPI (bid)				
Analysis group, n (%)	**Placebo**	**50 mcg**	**100 mcg**	**200 mcg**	**Combined**	**50/12.5 mcg**	**100/12.5 mcg**	**200/12.5 mcg**	**Combined**	**Total**
Randomised	275 (100)	129 (100)	276 (100)	146 (100)	551 (100)	129 (100)	274 (100)	146 (100)	549 (100)	1375 (100
Randomised, not treated	2 (<1)	0	2 (<1)	0	2 (<1)	1 (<1)	5 (2)	1 (<1)	7 (1)	11 (<1)
Full analysis set	272 (99)	128 (>99)	274 (>99)	146 (100)	548 (>99)	128 (>99)	267 (97)	145 (>99)	540 (98)	1360 (99
Completed study	220 (80)	121 (94)	257 (93)	135 (92)	513 (93)	121 (94)	262 (96)	136 (93)	519 (95)	1252 (91
Discontinued study	55 (20)	8 (6)	19 (7)	11 (8)	38 (7)	8 (6)	12 (4)	10 (7)	30 (5)	123 (9)
Adverse event	8 (3)	1 (<1)	4 (1)	0	5 (<1)	3 (2)	2 (<1)	2 (1)	7 (1)	20 (1)
Withdrawal by patient	9 (3)	3 (2)	6 (2)	3 (2)	12 (2)	2 (2)	3 (1)	2 (1)	7 (1)	28 (2)
Non-compliance to study medication	0	0	1 (<1)	1 (<1)	2 (<1)	0	0	0	0	2 (<1)
Protocol violation	2 (<1)	1 (<1)	3 (1)	2 (1)	6 (1)	0	0	1 (<1)	1 (<1)	9 (<1)
Disease progression	20 (7)	1 (<1)	1 (<1)	3 (2)	5 (<1)	0	1 (<1)	2 (1)	3 (<1)	28 (2)
Pregnancy	0	0	0	0	0	0	0	1 (<1)	1 (<1)	1 (<1)
Lost to follow-up	2 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	8 (<1)
Lack of efficacy	11 (4)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)	0	0	1 (<1)	15 (1)
Other	3 (1)	0	2 (<1)	0	2 (<1)	1 (<1)	5 (2)	1 (<1)	7 (1)	12 (<1)

Source: Module 5.3.5.3, Summary 1.1
bid=twice daily; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; n=number of patients.
Note: The denominator for calculating percentages was the number of randomised patients. Patient 30017_90014007 discontinued due to adverse event on 20 March 2015 before the fatal incidence on 23 April 2015. Therefore, the discontinuation reason was captured as adverse events, other than death. Patient is listed in adverse events leading to death (Study FSS-AS-30017, Listing 16.2.7.2).

The exclusion of less than 1% of the patients and approximately 9% discontinuations are not expected to have an impact on the outcome of the studies.

Outcomes and estimation

Study FSS-AS-301

Primary endpoints

All comparisons of interest were statistically significant for both co-primary endpoints following the fixed-sequence multiple testing procedure (results for the FAS are shown in the below Table). Results in the ITT and PP populations were nearly identical to those in the FAS. For both endpoints, improvements were greater in the FS MDPI and Fp MDPI groups than in the placebo group, and greater in the FS MDPI groups than in the Fp MDPI groups, supporting the additional benefit of the salmeterol xinafoate (Sx) in combination with fluticasone propionate (Fp). Serial spirometry results showed that the immediate improvements observed in the active treatment groups were sustained over the 12 hours of testing, and the PD profile was consistent with a twice-daily dosing regimen. Results were robust in supportive and sensitivity analyses. In subgroup analyses, results for active treatment groups were numerically superior to those for placebo for both endpoints and were generally comparable to findings for the overall FAS.

Table 17: (synopsis Study FSS-AS-301): Summary of Co-Primary Endpoint Analyses (FAS)

	Placebo	Fp MDPI 50 mcg BID	Fp MDPI 100 mcg BID	FS MDPI 50/12.5 mcg BID	FS MDPI 100/12.5 mcg BID
Change from baseline in trough morning FEV_1 at week 12					
Actual mean change	0.116 L	0.203 L	0.224 L	0.340 L	0.326 L
LS mean	0.053	0.172	0.204	0.319	0.315
Comparison to placebo		p=0.0132	p=0.0017	p=0.0000	p=0.0000
Comparison to Fp MDPI 50 mcg BID				p=0.0022	
Comparison to Fp MDPI 100 mcg BID				p=0.0166	p=0.0202
Standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12hr}$ at week 12					
LS mean 0-12hr	0.074	0.268	0.254	0.399	0.408
Comparison to placebo		p=0.0012	p=0.0020	p=0.0000	p=0.0000
Comparison to Fp MDPI 50 mcg BID				p=0.0322	
Comparison to Fp MDPI 100 mcg BID				p=0.0151	p=0.0076

Source: Summary 15.2.1.1.1, Summary 15.2.1.2.1, Summary 15.2.5.1.1, Summary 15.2.5.2.1, and Listing 16.2.6.1.
FAS = full analysis set; Fp MDPI = fluticasone propionate multidose dry powder inhaler; BID = twice daily; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; FEV_1 = forced expiratory volume in 1 second; LS = least squares; FEV_1 $AUEC_{0\text{-}12hr}$ = area under the effect curve for forced expiratory volume in 1 second from 0 to 12 hours

Comparisons of combination therapy with monotherapy were not controlled for multiplicity but indicated improvement for FS MDPI 50/12.5 mcg compared with Fp MDPI 50 mcg (p=0.0022) and Fp MDPI 100 mcg (p=0.0166) and for FS MDPI 100/12.5 mcg compared with Fp MDPI 100 mcg (p=0.0202) in Study FSS-AS-301 (Table 18).

Table 18: Primary Analysis of Change from Baseline in Trough FEV1 at Week 12 by Treatment Group (Full Analysis Set, Study FSS-AS-301)

Variable Statistic	Placebo (N=129)	Fp MDPI 50 mcg bid (N=128)	Fp MDPI 100 mcg bid (N=129)	FS MDPI 50/12.5 mcg bid (N=128)	FS MDPI 100/12.5 mcg bid (N=126)
Change in trough FEV_1 (L) at week 12					
n	129	128	129	128	126
LS mean	0.053	0.172	0.204	0.319	0.315
SE of LS mean	0.0350	0.0347	0.0340	0.0350	0.0352
95% CI	(-0.015, 0.122)	(0.104, 0.240)	(0.137, 0.271)	(0.250, 0.388)	(0.246, 0.385)

Variable Statistic	Placebo (N=129)	Fp MDPI 50 mcg bid (N=128)	Fp MDPI 100 mcg bid (N=129)	FS MDPI 50/12.5 mcg bid (N=128)	FS MDPI 100/12.5 mcg bid (N=126)
Comparison to placebo					
Difference of LS mean	—	0.119	0.151	0.266	0.262
95% CI	—	(0.025, 0.212)	(0.057, 0.244)	(0.172, 0.360)	(0.168, 0.356)
p-value	—	0.0132	0.0017	<0.0001	<0.0001
Comparison to Fp MDPI 50 mcg bid					
Difference of LS mean	—	—	NA	0.147	0.144
95% CI	—	—	—	(0.053, 0.242)	(0.049, 0.238)
p-value	—	—	—	0.0022	0.0028
Comparison to Fp MDPI 100 mcg bid					
Difference of LS mean	—	—	—	0.115	0.111
95% CI	—	—	—	(0.021, 0.210)	(0.017, 0.206)
p-value	—	—	—	0.0166	0.0202

Source: MAA 120 D Questions Table 12.1.
ANCOVA=analysis of covariance; bid=twice daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; Fp MDPI=fluticasone propionate multi-dose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LS=least squares; NA=not applicable; SE=standard error.
Note: n denotes the number of patients who contribute at least once to the analysis. The analysis is based on an ANCOVA model with adjustment for baseline FEV_1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment. Missing data are imputed using the modified baseline observation carried forward.

Secondary endpoints

Results of secondary efficacy analyses further support the conclusion that treatment with Fp MDPI and FS MDPI was associated with improved lung function and the additional benefit of combination therapy, as follows:

- Results for FS MDPI and Fp MDPI 100 mcg were statistically significantly superior to placebo for change from baseline in the weekly average of daily trough AM PEF over 12 weeks, change from baseline in the weekly average of total daily asthma symptom score over weeks 1 to 12, and change from baseline in the weekly average of total daily rescue medication use over weeks 1 to 12 (and there was a trend in favour of Fp MDPI 50 mcg for the latter 2 of these 3 endpoints). There was a trend in favour of each active treatment group relative to placebo for change from baseline in AQLQ(S).
- Combination therapy was statistically significantly superior to monotherapy for daily trough AM PEF, and numerically superior for the other endpoints.

- For withdrawal because of worsening asthma, only 7 patients overall met the criteria (4 patients in the placebo group, 0 patients in the FS MDPI 100/12.5 mcg group, and 3 in the other active treatment groups).
- Differentiation between Fp MDPI and FS MDPI treatments was evident, particularly for weekly average of the daily trough AM PEF.
- Results for the important secondary endpoint of time to 15% and 12% improvement from baseline in FEV_1 post-dose at TV1 (after the first dose) showed that FS MDPI was superior to placebo. Ad hoc analyses of time to onset of these improvement thresholds showed that improvements in asthma control occurred within 15 minutes of inhaled administration for approximately one-fifth of patients treated in the FS MDPI groups.

Other efficacy variables

Findings for other efficacy variables were consistent with the outcomes for the primary and secondary variables, including the following details:

- The proportions of patients who met asthma alert criteria were 24% in the placebo group compared with 7% to 15% in the active treatment groups, and there was apparent dose-associated separation within the Fp MDPI and FS MDPI treatments.
- Mean decreases in rescue medication use from baseline to day 14 were greater for FS MDPI and Fp MDPI than for placebo, and greater for FS MDPI than for Fp MDPI. This was also true at subsequent weeks and at endpoint. Dose-dependent differentiation within the Fp MDPI and FS MDPI groups was not evident.
- Change from baseline in the percentage of rescue-free, symptom-free, and asthma-control days was greater for FS MDPI than for Fp MDPI and placebo. Change from baseline for symptom-free and asthma-control days appeared to be dose-dependent for FS MDPI but not for Fp MDPI.
- Change from baseline for trough FVC and trough FEF_{25-75} supported the findings for FEV_1.
- The proportions of patients who experienced a clinically significant change from baseline in the AQLQ(S) were similar between placebo and Fp MDPI at just under half of patients, and the proportions for FS MDPI were slightly over half of patients. Dose-associated separation was observed for FS MDPI but not for FP MDPI.
- Change from baseline in ACT scores showed statistically significant differences in change from baseline for all active treatments compared with placebo. At each assessment and overall, the FS MDPI 100/12.5 mcg group had the smallest proportions of patients with ACT scores ≤19, and proportions were greatest for placebo. Effects appeared to be dose-dependent for FS MDPI but not Fp MDPI.

Study FSS-AS-30017

Primary endpoints

All comparisons of interest were statistically significant for both co-primary endpoints following the fixed-sequence multiple testing procedure when analysed for both the FAS and the ITT population (results for the FAS are shown in Table 19) and, with the exception of FS MDPI 100/12.5 mcg compared with Fp MDPI 200 mcg for trough FEV_1, for the PP population. For both endpoints, improvements were greater in the FS MDPI and Fp MDPI groups than in the placebo group, and greater in the FS MDPI groups than in the Fp MDPI groups, supporting the additional benefit of the Sx in combination with Fp. Serial spirometry results showed that the improvements observed in the active

treatment groups were sustained over the 12 hours of testing, and the PD profile was consistent with a twice-daily dosing regimen. Results were robust in supportive and sensitivity analyses. In subgroup analyses, results for active treatment groups were numerically superior to those for placebo for both endpoints and were generally comparable to findings for the overall FAS.

Table 19: (synopsis Study FSS-AS-30017): Summary of Co-Primary Endpoint Analyses (FAS)

	Placebo	Fp MDPI 100 mcg BID	Fp MDPI 200 mcg BID	FS MDPI 100/12.5 mcg BID	FS MDPI 200/12.5 mcg BID
Change from baseline in trough morning FEV_1 at week 12					
Actual mean change	0.090 L	0.108 L	0.203 L	0.277 L	0.290 L
LS mean	-0.004	0.119	0.179	0.271	0.272
Comparison to placebo		p=0.0047	p=0.0000	p=0.0000	p=0.0000
Comparison to Fp MDPI 100 mcg BID				p=0.0005	
Comparison to Fp MDPI 200 mcg BID				p=0.0356	p=0.0309
Standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12hr}$ at week 12					
LS mean 0-12hr	0.121	0.260	0.267	0.442	0.446
Comparison to placebo		p=0.01008	p=0.0084	p=0.0000	p=0.0000
Comparison to Fp MDPI 100 mcg BID				p=0.0010	
Comparison to Fp MDPI 200 mcg BID				p=0.0017	p=0.0009

Source: Summary 15.2.1.1.1, Summary 15.2.1.2.1, Summary 15.2.5.1.1, Summary 15.2.5.2.1, and Listing 16.2.6.1.
FAS = full analysis set; Fp MDPI = fluticasone propionate multidose dry powder inhaler; BID = twice daily; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; FEV_1 = forced expiratory volume in 1 second; LS = least squares; FEV_1 $AUEC_{0\text{-}12hr}$ = area under the effect curve for forced expiratory volume in 1 second from 0 to 12 hours

Comparisons of combination therapy with monotherapy were not controlled for multiplicity but indicated improvement for FS MDPI 100/12.5 mcg compared with Fp MDPI 100 mcg (p=0.0005) and Fp MDPI 200 mcg (p=0.0356) and for FS MDPI 200/12.5 mcg compared with Fp MDPI 200 mcg (p=0.0309) in Study FSS-AS-30017 (Table 20).

Table 20: Primary Analysis of Change from Baseline in Trough FEV1 at Week 12 by Treatment Group (Full Analysis Set, Study FSS-AS-30017)

Variable Statistic	Placebo (N=143)	Fp MDPI		FS MDPI	
		100 mcg bid (N=145)	200 mcg bid (N=146)	100/12.5 mcg bid (N=141)	200/12.5 mcg bid (N=145)
Change in trough FEV_1 (L) at week 12					
n	143	144	145	140	145
LS mean	-0.004	0.119	0.179	0.271	0.272
SE of LS mean	0.0312	0.0311	0.0308	0.0311	0.0307
95% CI	(-0.065, 0.057)	(0.058, 0.180)	(0.119, 0.240)	(0.210, 0.332)	(0.212, 0.333)

Variable Statistic	Placebo (N=143)	Fp MDPI		FS MDPI	
		100 mcg bid (N=145)	200 mcg bid (N=146)	100/12.5 mcg bid (N=141)	200/12.5 mcg bid (N=145)
Comparison to placebo					
Difference of LS mean	—	0.123	0.183	0.274	0.276
95% CI	—	(0.038, 0.208)	(0.098, 0.268)	(0.189, 0.360)	(0.191, 0.361)
p-value	—	0.0047	<0.0001	<0.0001	<0.0001
Comparison to Fp MDPI 100 mcg bid					
Difference of LS mean	—	—	NA	0.152	0.153
95% CI	—	—	—	(0.066, 0.237)	(0.068, 0.238)
p-value	—	—	—	0.0005	0.0004
Comparison to Fp MDPI 200 mcg bid					
Difference of LS mean	—	—	—	0.092	0.093
95% CI	—	—	—	(0.006, 0.177)	(0.009, 0.178)
p-value	—	—	—	0.0356	0.0309

Source: MAA 120 D Questions Table 12.3.
ANCOVA=analysis of covariance; bid=twice daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; Fp MDPI=fluticasone propionate multi-dose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LS=least squares; NA=not applicable; SE=standard error.
Note: n denotes the number of patients who contribute at least once to the analysis. The analysis is based on an ANCOVA model with adjustment for baseline FEV_1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment. Missing data are imputed using the modified baseline observation carried forward.

Results suggest some dose-associated differentiation between the higher and lower doses for Fp MDPI for trough AM and PM PEF over the 12-week treatment period, change from baseline in AQLQ(S) score and proportion of patients with an MID for AQLQ(S) or PAQLQ(S), and change from baseline in rescue medication use and in percentage of rescue-free days. Some differentiation was also evident for FEV_1, FEF 25-75, and FVC at each visit, mainly for Fp MDPI but also for FS MDPI to a lesser extent. Slight differentiation between the higher and lower doses for FS MDPI was evident for percentage of symptom-free days and percentage of asthma-control days.

Secondary endpoints

Results of secondary efficacy analyses further support the conclusion that treatment with Fp MDPI and FS MDPI was associated with improved lung function and the additional benefit of combination therapy, as follows:

- Results for FS MDPI and Fp MDPI were each statistically significantly superior to placebo for change from baseline in the weekly average of daily trough AM PEF over 12 weeks, change from baseline in the weekly average of total daily asthma symptom score over weeks 1 to 12, change from baseline in the weekly average of total daily rescue medication use over weeks 1 to 12, time to withdrawal for worsening asthma, and change from baseline in AQLQ(S).
- All comparisons of combination therapy to monotherapy showed statistically significant differences in favour of combination therapy for daily trough AM PEF; the comparison of FS MDPI 200/12.5 mcg with Fp MDPI 200 mcg was statistically significant for asthma symptom scores and for rescue medication use. Results for combination therapy were numerically superior to monotherapy for the other secondary endpoints except for time to withdrawal for worsening asthma.
- Twenty (14%) patients in the placebo group and 9 (1.6%) in all active treatment groups were withdrawn because of worsening asthma.
- Differentiation between Fp MDPI and FS MDPI treatments was evident for most secondary endpoints.
- Results for the important secondary endpoint of time to 15% and 12% improvement from baseline in FEV_1 postdose at TV1 (after the first dose) showed that FS MDPI was superior to placebo. Ad hoc analyses of time to onset of these improvement thresholds showed that improvements in asthma control occurred within 15 minutes of inhaled administration for 21% of patients treated with FS MDPI 100/12.5 mcg and for 34% of patients treated with FS MDPI 200/12.5 mcg.

Other efficacy variables

Findings for other efficacy variables were consistent with the outcomes for the primary and secondary variables, including the following details:

- The proportions of patients who met asthma alert criteria were 38% in the placebo group compared with 9% to 18% in the active treatment groups.
- Mean decreases in rescue medication use from baseline to day 14 were greater for FS MDPI and Fp MDPI than for placebo, and greater for FS MDPI than for Fp MDPI. This was also true at subsequent weeks and at endpoint. Dose-dependent differentiation within the Fp MDPI and FS MDPI groups was evident at all weeks.
- Change from baseline in the percentage of rescue-free, symptom-free, and asthma-control days was greater for FS MDPI than for Fp MDPI and placebo. Change from baseline for rescue-free days appeared to be dose-dependent for Fp MDPI, and change for symptom-free and asthma-control days appeared to be dose-dependent for FS MDPI but not for Fp MDPI.
- Change from baseline for trough FVC and trough FEF_{25-75} supported the findings for FEV_1.
- The proportions of patients who experienced a clinically significant change from baseline in the AQLQ(S) were lower for placebo (34%) than active treatment groups (38% to 48%).

- Change from baseline in ACT showed notable differences ($p<0.05$) from baseline for all active treatments compared with placebo. At each assessment and overall, the FS MDPI 100/12.5 mcg group had the smallest proportions of patients with ACT scores ≤19, and proportions were greatest for placebo.

Study FSS-AS-301 and Study FSS-AS-30017

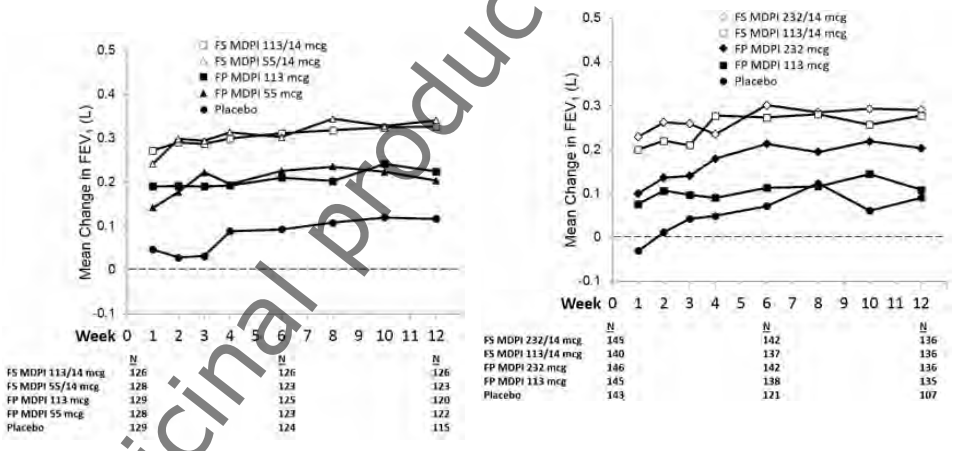
Primary efficacy endpoints in placebo-controlled Phase 3 asthma studies

All primary FEV_1 endpoint comparisons of interest as specified in the fixed-sequence multiple testing procedure were statistically significant ($p<0.05$). FS MDPI achieved greater increases from baseline FEV_1 in the comparisons between **FS** MDPI **50**/12.5 mcg and **Fp** MDPI **50** mcg, between **FS** MDPI **100**/12.5 mcg and all **3 Fp** MDPI doses, and between **FS** MDPI **200**/12.5 mcg and **Fp** MDPI **200** mcg, demonstrating, according to the applicant, the clinical benefit of adding salmeterol to Fp in the FS MDPI.

The improvement in FEV_1 was sustained over the 12-week duration of both studies. Benefit in lung function was demonstrated for all doses of FS MDPI, including the low dose strength of 50/12.5 mcg compared to placebo.

There was an apparent dose-dependent increase in trough FEV_1 following Fp MDPI monotherapy treatment in both studies that was more pronounced in **Study FSS-AS-30017 (**Figure 10**)**. No apparent trend in dose-dependency in trough FEV_1 was observed after FS MDPI combination treatment; this finding is likely due to the fixed dose of salmeterol in the FS MDPI treatment groups that masks any dose-response contribution from Fp.

Figure 10: Mean change from baseline in trough FEV_1 at each visit by treatment group (Study FSS-AS-301 and Study FSS-AS-30017)



	N	N	N
FS MDPI 113/14 mcg	126	126	126
FS MDPI 55/14 mcg	128	123	123
FP MDPI 113 mcg	129	125	120
FP MDPI 55 mcg	128	123	122
Placebo	129	124	115

	N	N	N
FS MDPI 232/14 mcg	145	142	136
FS MDPI 113/14 mcg	140	137	136
FP MDPI 232 mcg	146	142	136
FP MDPI 113 mcg	145	138	135
Placebo	143	121	107

Results of the primary endpoint analysis of standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 in both studies achieved statistical significance ($p<0.05$) in comparisons between all FS MDPI doses against corresponding Fp MDPI doses and both FS and Fp MDPI compared with placebo.

No dose-dependent trends were apparent after 12 weeks of treatment with FS MDPI. Relative to treatment visit 1 (TV1), serial spirometry findings at week 12 showed improvements in the FS MDPI treatment groups that were not seen in the placebo group; this was particularly apparent in **Study FSS-AS-30017** (Figure 11 and Figure 12). These serial spirometry results confirm that the bid dosing regimen is appropriate for FS MDPI.

Figure 11: Serial spirometry: mean change from baseline in FEV_1 (L) at treatment visit 1 (Left Panel) and week 12 (Right Panel) by time point and treatment group (Study FSS-AS-301)

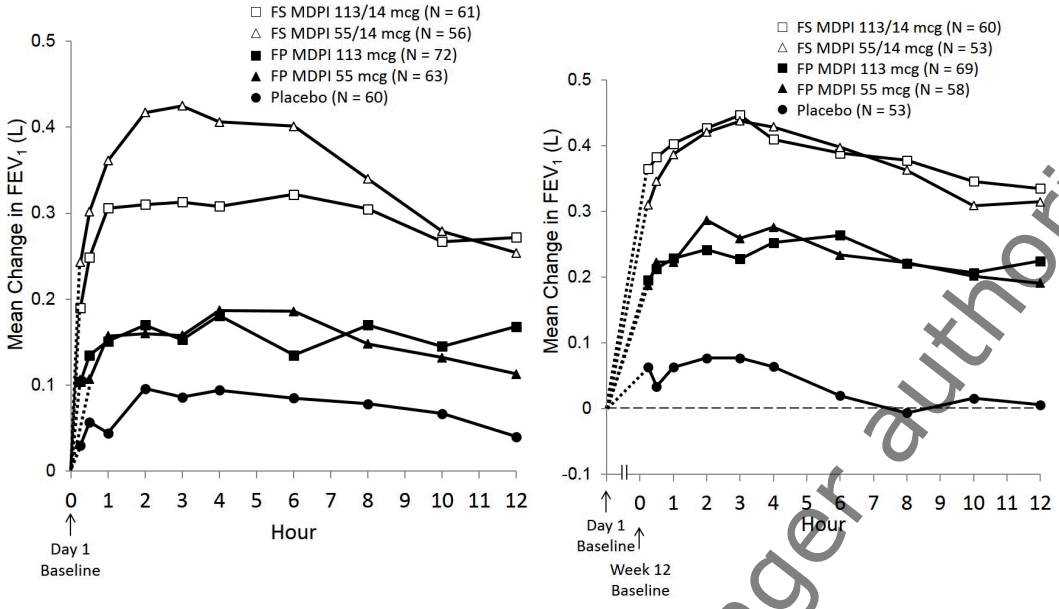
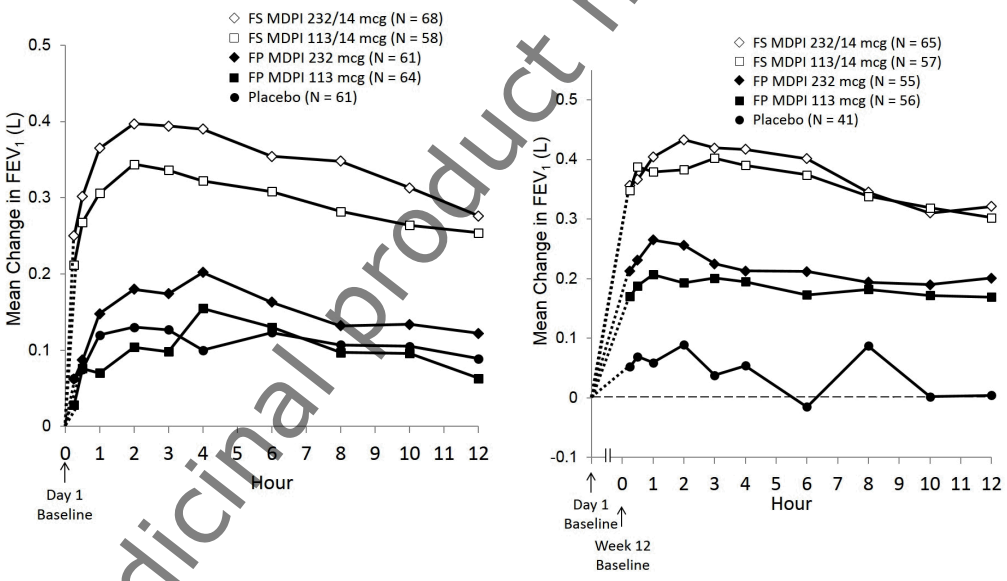


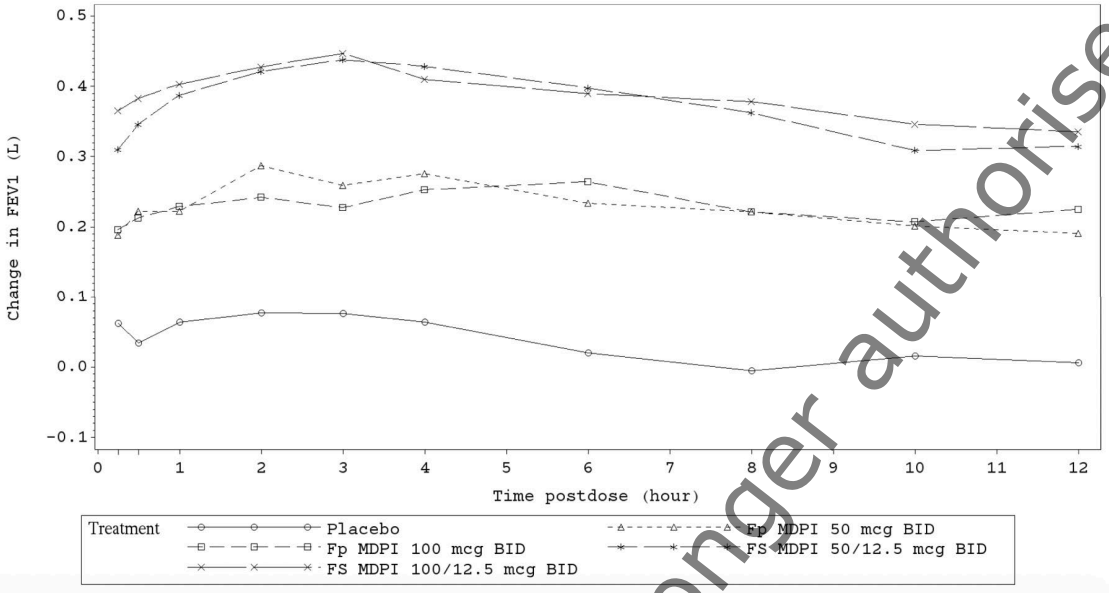
Figure 12: Serial spirometry: mean change from baseline in FEV_1 (L) at treatment visit 1 (left panel) and week 12 (right panel) by time point and treatment group (Study FSS-AS-30017)



Results for the standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ based on serial spirometry for combination therapy compared with monotherapy indicated that FS MDPI 100/12.5 mcg and 200/12.5 mcg doses were statistically significantly superior to Fp MDPI 100 and 200 mcg doses, respectively, and that FS MDPI 50/12.5 and 100/12.5 mcg doses were statistically significantly superior to Fp MDPI 50 and 100 mcg doses, respectively (Figure 13 and Figure 14 respectively). There were also improvements for FS MDPI 50/12.5 and 100/12.5 mcg doses compared with Fp MDPI 100 and 200 mcg doses, respectively. Results for the standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ based on

serial spirometry in the FS MDPI and Fp MDPI groups were statistically significantly superior to those in the placebo group.

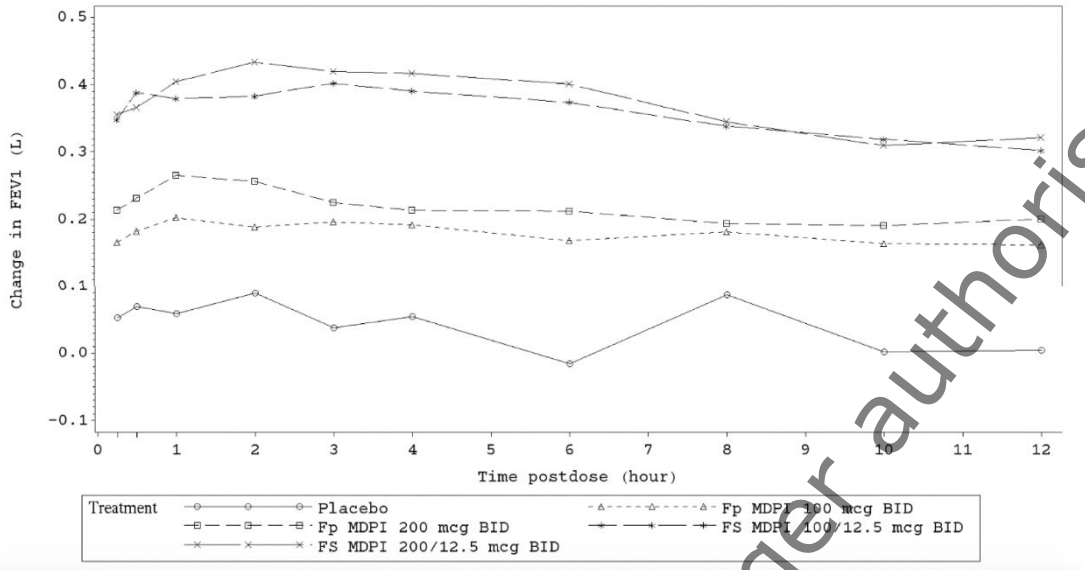
Figure 13: Serial Spirometry: Mean Change from Baseline in FEV1 (L) at Week 12 by Time Point and Treatment Group (Full Analysis Set, Study FSS-AS-301; Serial Spirometry Subset)



Source: Study FSS-AS-301 CSR, Figure 6.
bid=twice daily; CSR=clinical study report; FEV_1=forced expiratory volume in 1 second; Fp MDPI=fluticasone propionate multi-dose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler.

Change in FEV1 between Fp MDPI 100 mcg BID (squares □) and Fp MDPI 50 mcg BID (triangles Δ) showed practically no difference. This flat dose response curve for ICS is known from the literature and was presented by the applicant. There is practically no difference between FS MDPI 100/12.5 mcg BID (crosses x) and FS MDPI 50/12.5 (asterisks *).

Figure 14: Serial Spirometry: Mean Change from Baseline in FEV1 (L) at Week 12 by Time Point and Treatment Group (Full Analysis Set, Study FSS-AS-30017; Serial Spirometry Subset)



Source: Study FSS-AS-30017 CSR, Figure 6.
bid=twice daily; CSR=clinical study report; FEV_1=forced expiratory volume in 1 second; Fp MDPI=fluticasone propionate multi-dose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler.

Overall, in both studies, all comparisons of interest were statistically significant for both co-primary endpoints following the fixed-sequence multiple testing procedure when analysed for both the FAS and ITT population. For both endpoints, improvements were greater in the FS MDPI and Fp MDPI groups. Serial spirometry results showed that the immediate improvements observed in the active treatment groups were sustained over the 12 hours of testing, and the PD profile was consistent with a bid dosing regimen. Results were robust in supportive and sensitivity analyses.

Secondary efficacy endpoints in placebo-controlled Phase 3 asthma studies

Secondary efficacy variables were analysed using the FAS. Because all primary endpoint comparisons as specified in the fixed-sequence multiple testing procedure were statistically significant, inferential testing was extended to the secondary efficacy endpoints. The secondary efficacy results for Studies FSS-AS-301 and FSS-AS-30017 are shown in Table 21.

Table 21: Mean values for secondary efficacy variables (Study FSS-AS-301 and Study FSS-AS-30017)

Efficacy variable[a]	Study FSS-AS-301					Study FSS-AS-30017				
		Fp MDPI		FS MDPI			Fp MDPI		FS MDPI	
	Placebo (N=129)	50 mcg bid (N=128)	100 mcg bid (N=129)	50/12.5 mcg bid (N=128)	100/12.5 mcg bid (N=126)	Placebo (N=143)	100 mcg bid (N=145)	200 mcg bid (N=146)	100/12.5 mcg bid (N=141)	200/12.5 mcg bid (N=145)
Weekly average of the daily trough morning PEF (L/min)										
Baseline	357	363	359	360	352	351	339	345	357	343
Change from baseline	3	14	17	29	28	-14	7	9	19	23
Weekly average of the total daily asthma symptom score										
Baseline	0.796	0.825	0.782	0.778	0.777	0.881	0.804	0.900	0.950	0.936
Change from baseline	-0.153	-0.321	-0.358	-0.362	-0.400	-0.061	-0.284	-0.278	-0.434	-0.436
Weekly average of the total daily use of albuterol/salbutamol inhalation aerosol (puff)										
Baseline	1.4	1.3	1.2	1.2	1.1	1.7	1.6	1.8	2.0	1.9
Change from baseline	-0.2	-0.5	-0.6	-0.8	-0.7	0.1	-0.4	-0.7	-1.1	-1.0
Time to patient withdrawal for worsening asthma (days)										
Patients	129	128	129	128	126	143	145	146	141	145
Events (%)	4 (3)	1 (<1)	1 (<1)	1 (<1)	0	20 (14)	1 (<1)	3 (2)	1 (<1)	4 (3)
AQLQ(S) score										
Baseline	4.921	5.151	5.025	5.142	4.991	4.924	5.024	4.941	4.899	5.047
Change from baseline	0.280	0.517	0.609	0.516	0.838	-0.096	0.279	0.355	0.601	0.476

[a] Change from baseline=change from baseline to endpoint.

AQLQ(S)=Asthma Quality of Life Questionnaire with Standardised Activities; bid=twice daily; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; PEF=peak expiratory flow.

Note: Doses shown are nominal doses.

Ancillary analyses

Analysis of Change From Baseline in Trough FEV_1 at Week 12 and Standardised Baseline-Adjusted FEV_1 $AUEC_{0-12h}$ From Serial Spirometry (Side by Side Comparison)

The change from baseline in trough FEV_1 over the 12-week treatment period is shown in Figure 1 (Study FSS-AS-301) and Figure 2 (Study FSS-AS-30017). The mean treatment differences in the change from baseline in trough FEV_1 for the Fp MDPI and FS MDPI treatment groups versus placebo are shown graphically in Figure 15. Statistical significance ($p<0.05$) was achieved in all FS MDPI doses compared to placebo.

In the comparison of FS MDPI 50/12.5 mcg compared to Fp MDPI 50 mcg, FS MDPI 100/12.5 mcg compared to all 3 Fp MDPI doses, and for FS MDPI 200/12.5 mcg compared to Fp MDPI 200 mcg, FS MDPI showed an improvement, with greater increases from baseline FEV_1 compared to Fp MDPI (unadjusted $p<0.05$).

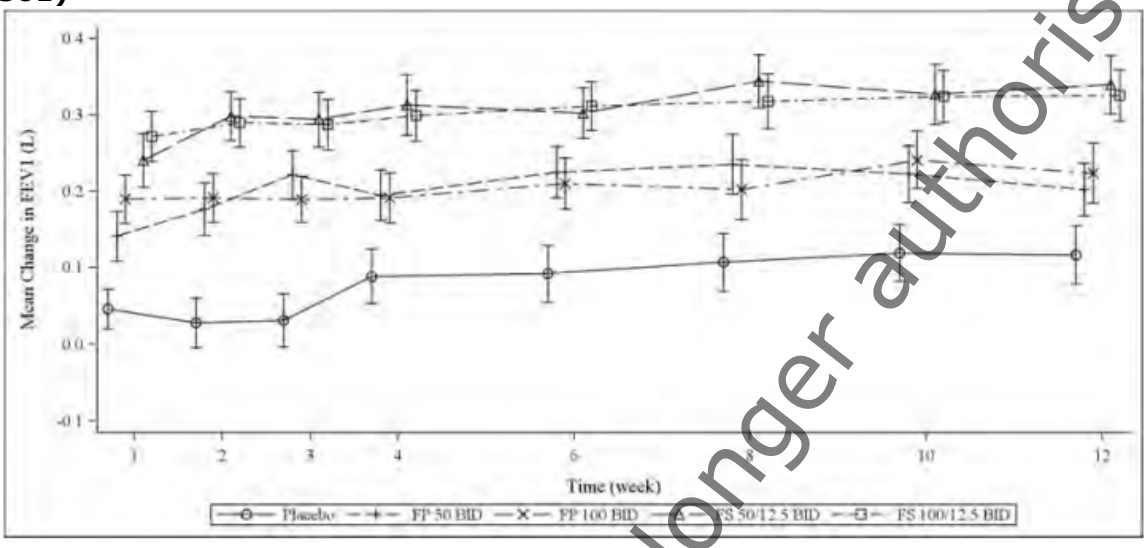
The mean treatment differences in the change from baseline in trough FEV_1 for Fp MDPI versus FS MDPI are shown graphically in Figure 16. In the comparison of FS MDPI 50/12.5 mcg to Fp MDPI 50 mcg, FS MDPI 100/12.5 mcg to all 3 Fp MDPI doses, and FS MDPI 200/12.5 mcg to Fp MDPI 200 mcg, FS MDPI showed an improvement, with greater increases from baseline FEV_1 compared to Fp MDPI (unadjusted $p<0.05$).

There was an apparent dose-dependent increase in trough FEV_1 following Fp MDPI monotherapy treatment in both studies that was more pronounced in Study FSS-AS-30017. No trends to dose dependency were observed following FS MDPI combination treatment for FEV_1. Treatment with Fp

MDPI 100 mcg resulted in similar differences from placebo in trough FEV_1 in both studies (LS means of 0.151 L in FSS-AS-301 and 0.123 L in FSS-AS-30017).

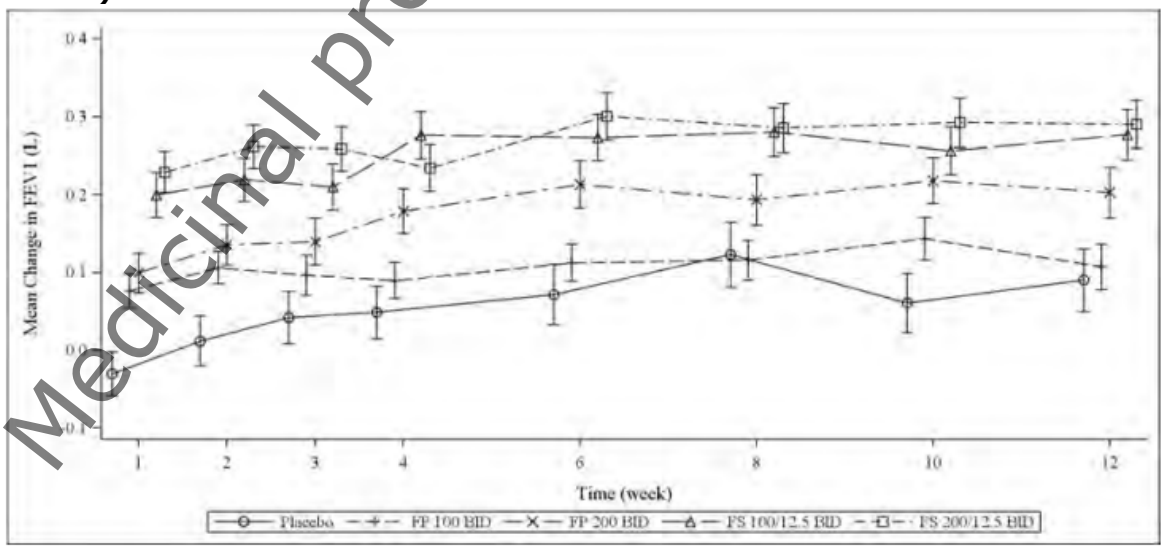
Change from baseline in trough FEV_1 at week 12 in the 2 Phase 3 studies (FSS-AS-301 and FSS-AS-30017) are presented for the ITT population and are almost identical to the results for the FAS.

Figure 15: (Summary of Clinical Efficacy): Mean (+/- SE) Change from Baseline in Trough FEV_1 at Each Visit by Treatment Group (Full Analysis Set, Study FSS-AS-301)



Source: Adhoc Figure 31.1.
bid=twice daily; FEV_1=forced expiratory volume in 1 second; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; Fp MDPI=fluticasone propionate multidose dry powder inhaler; SE=standard error. Note: Figure presents observed values; no missing data imputation was performed. Over the 12-week treatment period, proportionally more patients in the placebo group (13%) discontinued treatment than patients in the FS MDPI treatment groups (2% to 6%). This disparity was due to discontinuations due to adverse events (5% for patients in the placebo group versus ≤2% for patients in the FS MDPI groups), lack of efficacy (3% versus <1%, respectively), and disease progression (2% versus 0%, respectively).

Figure 16: (Summary of Clinical Efficacy): Mean (+/- SE) Change from Baseline in Trough FEV_1 at Each Visit by Treatment Group (Full Analysis Set, Study FSS-AS-30017)

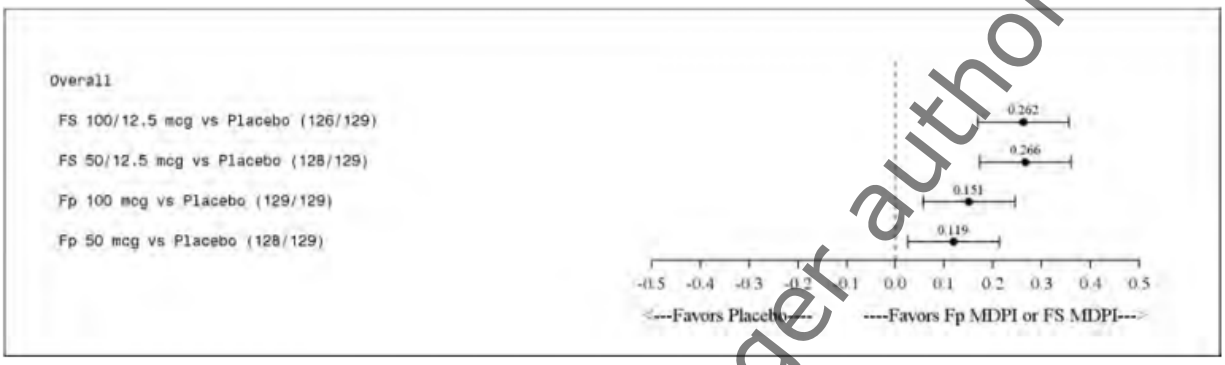


bid=twice daily; FEV_1 =forced expiratory volume in 1 second; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; Fp MDPI=fluticasone propionate multidose dry powder inhaler; SE=standard error. Note: Figure

presents observed values; no missing data imputation was performed. Over the 12-week treatment period, proportionally more patients in the placebo group (26%) discontinued treatment than patients in the FS MDPI treatment groups (6% to 7%). This disparity was due to discontinuations due to disease progression (12% for patients in the placebo group versus ≤1% for patients in the FS MDPI groups), lack of efficacy (5% versus 0%, respectively), and withdrawal by patient (5% versus 1% to 2%, respectively).

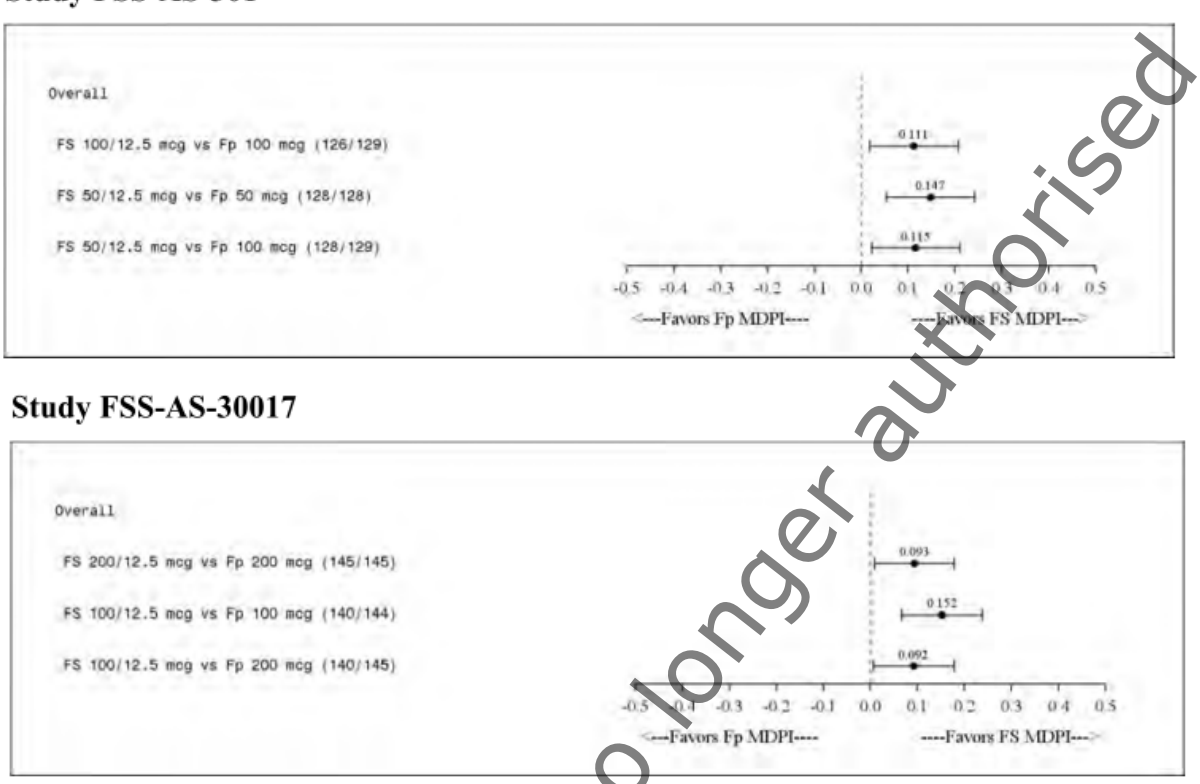
Figure 17: (Summary of Clinical Efficacy): Change from Baseline Trough FEV_1 (L) at Week 12 Treatment Effect Analysis; Comparison of FS MDPI and Fp MDPI With Placebo (Full Analysis Set)

Study FSS-AS-301



CI=confidence interval; FEV_1 =forced expiratory volume in 1 second; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; Fp MDPI=fluticasone propionate multidose dry powder inhaler. Note: Forest plot is the mean treatment difference and 95% CI; numbers in parentheses are sample size respective to the 2 compared treatment groups.

Figure 18: (Summary of Clinical Efficacy): Change from Baseline Trough FEV_1 (L) at Week 12 Treatment Effect Analysis; Comparison of FS MDPI With Fp MDPI (Full Analysis Set)



CI=confidence interval; FEV_1 =forced expiratory volume in 1 second; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; Fp MDPI=fluticasone propionate multidose dry powder inhaler. Note: Forest plot is the mean treatment difference and 95% CI; numbers in parentheses are sample size respective to the 2 compared treatment groups.

2.5.2.2. Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22: Summary of efficacy for trial FSS-AS-301

Title: A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult Patients with Persistent Asthma Symptomatic Despite Low-dose or Mid-dose Inhaled Corticosteroid Therapy	
Study identifier	Study FSS-AS-301, EudraCT Number: 2014-001149-25
Design	This was a 12-week, multicentre, randomised, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of treatment with 1 inhalation twice a day of Fp MDPI 50 mcg, Fp MDPI 100 mcg, FS MDPI 50/12.5 mcg, or FS MDPI 100/12.5 mcg

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks of 1 inhalation twice a day 14 to 21 days: 1 inhalation twice a day from single-blind placebo MDPI and 1 puff twice a day from open-label QVAR Follow-Up (in person or via telephone) 7 ±2 days after TV9/ET for safety and monitoring
Hypothesis	Superiority		
Treatments groups	Fp MDPI 50 mcg		Fluticasone Propionate Multidose Dry Powder Inhaler, BID, total daily dose 100mcg, Randomised 129, FAS 128
	Fp MDPI 100 mcg		Fluticasone Propionate Multidose Dry Powder Inhaler, BID, total daily dose 200mcg, Randomised 130, FAS 129
	FS MDPI 50/12.5 mcg		Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler, BID, total daily dose 100/25mcg, Randomised 129, FAS 128
	FS MDPI 100/12.5 mcg		Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler, BID, total daily dose 200/25mcg, Randomised 129, FAS 126
	Placebo MDPI		Placebo Multidose Dry Powder Inhaler, BID, total daily dose 0mcg, Randomisd 130, FAS 129
Endpoints and definitions	Primary endpoins in order of fixed sequence multiple	1) FEV1 AUEC0-12h [FS100/12.5 vs Fp 100]	Standardised baseline-adjusted FEV1 AUEC0-12h at week 12 for FS MDPI 100/12.5 mcg BID vs. Fp MDPI 100 mcg BID
		2) FEV1 AUEC0-12h [FS50/12.5 vs Fp 50]	Standardised baseline-adjusted FEV1 AUEC0-12h at week 12 for FS MDPI 50/12.5 mcg BID vs. Fp MDPI 50 mcg BID
		3) FEV1 AUEC0-12h [FS100/12.5 vs Placebo]	Standardised baseline-adjusted FEV1 AUEC0-12h at week 12 for FS MDPI 100/12.5 mcg BID vs. Placebo
		4) FEV1 AUEC0-12h [FS50/12.5 vs Placebo]	Standardised baseline-adjusted FEV1 AUEC0-12h at week 12 for FS MDPI 50/12.5 mcg BID vs. Placebo
		5) Trough FEV1 [FS100/12.5 vs Placebo]	Change from baseline in trough FEV1 at week 12 for FS MDPI 100/12.5 mcg BID vs. Placebo
		6) Trough FEV1 [FS50/12.5 vs Placebo]	Change from baseline in trough FEV1 at week 12 for FS MDPI 50/12.5 mcg BID vs. Placebo

		7) Trough FEV1 [Fp100 vs Placebo]	Change from baseline in trough FEV1 at week 12 for Fp100 mcg BID vs. Placebo
		8) Trough FEV1 [Fp50 vs Placebo]	Change from baseline in trough FEV1 at week 12 for Fp50 mcg BID vs. Placebo
	Secondary endpoints under partial Type I error control: ➢ Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period ➢ Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 to 12 ➢ Change from baseline in the weekly average of total daily (24-hour) use of albuterol /salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12 ➢ Time to patient withdrawal for worsening asthma during the 12-week treatment period ➢ Change from baseline in the AQLQ(S) (patients ≥18 years of age only) score at endpoint		
Database lock	Study Completion Date (last patient completed): 21 September 2015		

Results and Analysis

Analysis description	**Primary Analysis**					
Analysis population and time point description	The full analysis set (FAS) included all patients in the ITT population who received at least 1 dose of study drug and had at least 1 post baseline trough FEV1 assessment.					
Descriptive statistics and estimate variability	Treatment group	Placebo	Fp50 BID	Fp100 BID	FS50/ 12.5 BID	FS100/ 12.5 BID
	Number of subjects (FAS)	129	128	129	128	126
	Primary Analysis of Change from Baseline in Trough FEV1 at Week 12, LS mean (95%CI)	0.053 (-0.015, 0.122)	0.172 (0.104, 0.240)	0.204 (0.137, 0.271)	0.319 (0.250, 0.388)	0.315 (0.246, 0.385)
	Number of subjects (FAS; Serial Spirometry subset	60	63	72	56	61
	Primary analysis of Standardised Baseline-Adjusted FEV1 AUEC0-12hr (L) at Week 12, LS mean (95%CI)	0.074 (-0.022, 0.170)	0.268 (0.178, 0.358)	0.254 (0.169, 0.339)	0.399 (0.305, 0.493)	0.408 (0.317, 0.500)
Effect estimate per comparison	1) FEV1 AUEC0-12h	Comparison groups			FS100/12.5 vs Fp 100	
		Difference in LS mean			0.154	
		95%CI			(0.041, 0.267)	
		P-value (ANCOVA)			0.0076	

	2) FEV1 AUEC0-12h [FS50/12.5 vs Fp 50]	Comparison groups	FS50/12.5 vs Fp 50
		Difference in LS mean	0.131
		95%CI	(0.011, 0.250)
		P-value (ANCOVA)	0.0322
	3) FEV1 AUEC0-12h [FS100/12.5 vs Placebo]	Comparison groups	FS100/12.5 vs Placebo
		Difference in LS mean	0.335
		95%CI	(0.216, 0.453)
		P-value (ANCOVA)	0.0000
	4) FEV1 AUEC0-12h [FS50/12.5 vs Placebo]	Comparison groups	FS50/12.5 vs Placebo
		Difference in LS mean	0.325
		95%CI	0.203, 0.447)
		P-value (ANCOVA)	0.0000
	5) Trough FEV1 [FS100/12.5 vs Placebo]	Comparison groups	FS100/12.5 vs Placebo
		Difference in LS mean	0.262
		95%CI	(0.168, 0.356)
		P-value (ANCOVA)	0.0000
	6) Trough FEV1 [FS50/12.5 vs Placebo]	Comparison groups	FS50/12.5 vs Placebo
		Difference in LS mean	0.266
		95%CI	(0.172, 0.360)
		P-value (ANCOVA)	0.0000
	7) Trough FEV1 [Fp100 vs Placebo]	Comparison groups	Fp100 vs Placebo
		Difference in LS mean	0.151
		95%CI	(0.057, 0.244)
		P-value (ANCOVA)	0.0017
	8) Trough FEV1 [Fp50 vs Placebo]	Comparison groups	Fp50 vs Placebo
		Difference in LS mean	0.119
		95%CI	(0.025, 0.212)
		P-value (ANCOVA)	0.0132
Notes	The primary endpoint has been met. Fp100 and FS groups showed statistically significant improvement vs Placebo in terms of PEF, asthma score and use of albuterol/salbutamol inhalation aerosol. Fp50 showed a positive trend but did not reach statistical significance. No patients in the FS100 withdrew for worsening asthma during the 12-Week treatment period, and only 1 from Fp50, Fp100 and DS50 compared to 4 in the Placebo group. Change from Baseline in the AQLQ(S) Score was significant for FS groups vs Placebo. A positive trend was observed for Fp groups.		

Table 23: Summary of efficacy for trial FSS-AS-30017

Title: A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult Patients with Persistent Asthma Symptomatic Despite Inhaled Corticosteroid Therapy

Study identifier	Study FSS-AS-30017, EudraCT Number: 2014-000923-25		
Design	This was a 12-week, multicentre, randomised, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of treatment with 1 inhalation twice a day of Fp MDPI 100 mcg, Fp MDPI 200 mcg, FS MDPI 100/12.5 mcg, or FS MDPI 200/12.5 mcg		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks of 1 inhalation twice a day 14 to 21 days: 1 inhalation twice a day from single-blind Fp MDPI 50 mcg Follow-Up (in person or via telephone) 7 ±2 days after TV9/ET for safety and monitoring	
Hypothesis	Superiority		
Treatments groups	Fp MDPI 100 mcg	Fluticasone Propionate Multidose Dry Powder Inhaler, BID, total daily dose 200mcg, Randomised 146, FAS 145	
	Fp MDPI 200 mcg	Fluticasone Propionate Multidose Dry Powder Inhaler, BID, total daily dose 400mcg, Randomised 146, FAS 146	
	FS MDPI 100/12.5 mcg	Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler, BID, total daily dose 200/25mcg, Randomised 145, FAS 141	
	FS MDPI 200/12.5 mcg	Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler, BID, total daily dose 400/25mcg, Randomised 146, FAS 145	
	Placebo MDPI	Placebo Multidose Dry Powder Inhaler, BID, total daily dose 0mcg, Randomisd 145, FAS 143	
Endpoints and definitions	Primary endpoints in order of fixed sequence	1) FEV1 AUEC0-12h [FS200/12.5 vs Fp 200]	Standardised baseline-adjusted FEV1 AUEC0-12h at week 12 for FS MDPI 200/12.5 mcg BID vs. Fp MDPI 200 mcg BID
		2) FEV1 AUEC0-12h [FS100/12.5 vs Fp 100]	Standardised baseline-adjusted FEV1 AUEC0-12h at week 12 for FS MDPI 100/12.5 mcg BID vs. Fp MDPI 100 mcg BID
		3) FEV1 AUEC0-12h [FS200/12.5 vs Placebo]	Standardised baseline-adjusted FEV1 AUEC0-12h at week 12 for FS MDPI 200/12.5 mcg BID vs. Placebo
		4) FEV1 AUEC0-12h [FS100/12.5 vs Placebo]	Standardised baseline-adjusted FEV1 AUEC0-12h at week 12 for FS MDPI 100/12.5 mcg BID vs. Placebo

		5) Trough FEV1 [FS200/12.5 vs Placebo]	Change from baseline in trough FEV1 at week 12 for FS MDPI 200/12.5 mcg BID vs. Placebo
		6) Trough FEV1 [FS100/12.5 vs Placebo]	Change from baseline in trough FEV1 at week 12 for FS MDPI 100/12.5 mcg BID vs. Placebo
		7) Trough FEV1 [Fp200 vs Placebo]	Change from baseline in trough FEV1 at week 12 for Fp200 mcg BID vs. Placebo
		8) Trough FEV1 [Fp100 vs Placebo]	Change from baseline in trough FEV1 at week 12 for Fp100 mcg BID vs. Placebo
	Secondary endpoints under partial Type I error control: ➢ Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period ➢ Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 to 12 ➢ Change from baseline in the weekly average of total daily (24-hour) use of albuterol /salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12 ➢ Time to patient withdrawal for worsening asthma during the 12-week treatment period ➢ Change from baseline in the AQLQ(S) (patients ≥18 years of age only) score at endpoint		
Database lock	Study Completion Date (last patient completed): 26 September 2015		

Results and Analysis

Analysis description	**Primary Analysis**					
Analysis population and time point description	The full analysis set (FAS) included all patients in the ITT population who received at least 1 dose of study drug and had at least 1 post baseline trough FEV1 assessment.					
Descriptive statistics and estimate variability	Treatment group	Placebo	Fp100 BID	Fp200 BID	FS100/ 12.5 BID	FS200/ 12.5 BID
	Number of subjects (FAS)	143	145	146	141	145
	Primary Analysis of Change from Baseline in Trough FEV1 at Week 12, LS mean (95%CI)	-0.004 (-0.065, 0.057)	0.119 (0.058, 0.180)	0.179 (0.119, 0.240)	0.271 (0.210, 0.332)	0.272 (0.212, 0.333)
	Number of subjects (FAS; Serial Spirometry subset	61	64	61	58	68

	Primary analysis of Standardised Baseline-Adjusted FEV1 AUEC0-12hr (L) at Week 12, LS mean (95%CI)	0.121 (0.028, 0.214)	0.260 (0.169, 0.351)	0.267 (0.175, 0.359)	0.442 (0.345, 0.540)	0.446 (0.355, 0.538)

Effect estimate per comparison	1) FEV1 AUEC0-12h	Comparison groups	FS200/12.5 vs Fp 200
		Difference in LS mean	0.179
		95%CI	(0.074, 0.285)
		P-value (ANCOVA)	0.0009
	2) FEV1 AUEC0-12h [FS100/12.5 vs Fp 100]	Comparison groups	FS100/12.5 vs Fp 100
		Difference in LS mean	0.182
		95%CI	(0.074, 0.291)
		P-value (ANCOVA)	0.0010
	3) FEV1 AUEC0-12h [FS200/12.5 vs Placebo]	Comparison groups	FS200/12.5 vs Placebo
		Difference in LS mean	0.326
		95%CI	(0.221, 0.431)
		P-value (ANCOVA)	0.0000
	4) FEV1 AUEC0-12h [FS100/12.5 vs Placebo]	Comparison groups	FS100/12.5 vs Placebo
		Difference in LS mean	0.322
		95%CI	(0.212, 0.432)
		P-value (ANCOVA)	0.0000
	5) Trough FEV1 [FS200/12.5 vs Placebo]	Comparison groups	FS200/12.5 vs Placebo
		Difference in LS mean	0.276
		95%CI	(0.191, 0.361)
		P-value (ANCOVA)	0.0000
	6) Trough FEV1 [FS100/12.5 vs Placebo]	Comparison groups	FS100/12.5 vs Placebo
		Difference in LS mean	0.274
		95%CI	(0.189, 0.360)
		P-value (ANCOVA)	0.0000
	7) Trough FEV1 [Fp200 vs Placebo]	Comparison groups	Fp200 vs Placebo
		Difference in LS mean	0.183
		95%CI	(0.098, 0.268)
		P-value (ANCOVA)	0.0000
	8) Trough FEV1 [Fp100 vs Placebo]	Comparison groups	Fp50 vs Placebo
		Difference in LS mean	0.123
		95%CI	(0.038, 0.208)
		P-value (ANCOVA)	0.0047

Notes	The primary endpoint has been met. Fp and FS groups showed statistically significant improvement vs Placebo in terms of PEF, and there was a statistically significant improvement of FS200/12.5 vs Fp200, and FS100/12.5 vs Fp100. Fp and FS groups showed statistically significant improvement vs Placebo in terms of asthma score, and there was a statistically significant improvement of FS200/12.5 vs Fp200, but not for FS100/12.5 vs Fp100. Fp and FS groups showed statistically significant improvement vs Placebo in terms of albuterol/salbutamol inhalation aerosol use, and there was a statistically significant improvement of FS200/12.5 vs Fp200, but not for FS100/12.5 vs Fp100. 20 patients in the Placebo group withdrew for worsening asthma during the 12-Week treatment period, and only 1 from Fp100, 3 in Fp200, 1 in FS100/12.4 and 4 in FS200/12.5. Change from Baseline in the AQLQ(S) Score was significant for FS and Fp groups vs Placebo.

2.5.2.3. Analysis performed across trials (pooled analyses and meta-analysis)

Pooled data from **Studies FSS-AS-301** and **FSS-AS-30017** by dose group showed similar baseline trough FEV_1 values across all FS MDPI and placebo groups. At week 12, all FS MDPI dose groups showed greater increases in mean change trough FEV_1 (0.340, 0.300, and 0.290 L in the 50/12.5, 100/12.5, and 200/12.5 mcg groups, respectively) than the placebo group (0.104 L). At week 12, the increase in mean baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ was similar (0.366, 0.356, and 0.369 L) in the FS MDPI 50/12.5, 100/12.5, and 200/12.5 mcg groups, respectively. All FS MDPI dose groups showed greater increases in mean baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ than the corresponding Fp MDPI groups (0.212, 0.192, and 0.194 L in the 50, 100, and 200 mcg groups, respectively) and the placebo group (0.032 L).

Data from Studies **FSS-AS-301** and **FSS-AS-30017** were also pooled for the same subgroups (sex, age, race, and geographic region); a summary of patient subgroups by treatment group for the FAS (pooled Phase 3 studies) is provided in Table 28 and further details on the results of the subgroup analyses are provided below.

The majority of patients were 18 to 64 years of age, from the US, female, and white. Overall, treatment effects were variable due to the small sample size and baseline imbalances in some groups. Improvement in lung function was consistently observed across majority of subgroups following treatment with FS MDPI with greater effects observed in the FS MDPI relative to the Fp MDPI groups. The forest plots illustrate that consistent differences are demonstrated in the subgroup categories (e.g. "Female," "Male," "White," "Black," etc.) for FS MDPI versus placebo, and for FS MDPI versus Fp MDPI. This provided evidence that no important interactions were present in any subgroups with reasonable sample sizes.

Table 24: (Summary of Clinical Efficacy): Patient Subgroups by Treatment Group (Full Analysis Set)

Variable Statistic	Placebo (N=272)	Fp MDPI				FS MDPI				Total (N=1360)
		50 mcg bid (N=128)	100 mcg bid (N=274)	200 mcg bid (N=146)	Combined (N=548)	50/12.5 mcg bid (N=128)	100/12.5 mcg bid (N=267)	200/12.5 mcg bid (N=145)	Combined (N=540)	
Sex, n (%)										
Male	113 (42)	53 (41)	106 (39)	58 (40)	217 (40)	57 (45)	118 (44)	58 (40)	233 (43)	563 (41)
Female	159 (58)	75 (59)	168 (61)	88 (60)	331 (60)	71 (55)	149 (56)	87 (60)	307 (57)	797 (59)
Age group, n (%)										
12 to 17	22 (8)	13 (10)	27 (10)	10 (7)	50 (9)	19 (15)	24 (9)	12 (8)	55 (10)	127 (9)
18 to 64	225 (83)	92 (72)	224 (82)	119 (82)	435 (79)	96 (75)	221 (83)	114 (79)	431 (80)	1091 (80)
65+	25 (9)	23 (18)	23 (8)	17 (12)	63 (11)	13 (10)	22 (8)	19 (13)	54 (10)	142 (10)
Race group, n (%)										
White	222 (82)	106 (83)	202 (74)	116 (79)	424 (77)	108 (84)	210 (79)	124 (86)	442 (82)	1088 (80)
Black	44 (16)	18 (14)	61 (22)	23 (16)	102 (19)	19 (15)	48 (18)	20 (14)	87 (16)	233 (17)
Other	6 (2)	4 (3)	11 (4)	7 (5)	22 (4)	1 (<1)	9 (3)	1 (<1)	11 (2)	39 (3)
Geographical region, n (%)										
USA	150 (55)	70 (55)	164 (60)	81 (55)	315 (57)	67 (52)	159 (60)	88 (61)	314 (58)	779 (57)
non-USA	122 (45)	58 (45)	110 (40)	65 (45)	233 (43)	61 (48)	108 (40)	57 (39)	226 (42)	581 (43)

Source: Module 5.3.5.3, Summary 2.2

bid=twice daily; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; n=number of patients with an observation; N=number of patients; USA=United States of America.

Table 25: (Summary of Clinical Efficacy): Summary of Actual Values and Change From Baseline in Trough FEV_1 at Week 12 by FS MDPI Treatment Group and Age Group (Full Analysis Set – Pooled Phase 3 Studies)

Age group	12-17				18-64				65+			
Timepoint Statistic	Placebo	50/12.5 mcg bid	100/12.5 mcg bid	200/12.5 mcg bid	Placebo	50/12.5 mcg bid	100/12.5 mcg bid	200/12.5 mcg bid	Placebo	50/12.5 mcg bid	100/12.5 mcg bid	200/12.5 mcg bid
Baseline												
n	22	19	24	12	225	96	220	114	25	13	22	19
Mean (SD)	2.330 (0.3671)	2.717 (0.4626)	2.341 (0.5513)	2.598 (0.5210)	2.218 (0.6261)	2.294 (0.6556)	2.193 (0.5860)	2.131 (0.6372)	1.476 (0.3273)	1.749 (0.4249)	1.599 (0.3095)	1.470 (0.3322)
Median	2.348	2.550	2.255	2.425	2.115	2.200	2.145	1.988	1.505	1.765	1.550	1.510
Min, max	1.555, 3.075	2.085, 3.515	1.580, 3.775	1.810, 3.695	0.920, 3.910	1.015, 3.870	1.145, 3.995	0.975, 3.740	0.765, 2.065	1.165, 2.470	1.090, 2.495	0.840, 2.350
Week 12 change												
n	22	19	24	12	180	93	216	105	20	11	22	19
Mean (SD)	0.90 (0.3541)	0.602 (0.5332)	0.565 (0.4894)	0.474 (0.5625)	0.113 (0.4377)	0.317 (0.3957)	0.271 (0.3641)	0.295 (0.3450)	0.038 (0.1718)	0.079 (0.2162)	0.302 (0.2631)	0.149 (0.1827)
Median	0.005	0.465	0.553	0.375	0.040	0.240	0.218	0.260	-0.035	0.020	0.280	0.140
Min, max	-0.850, 0.840	0.085, 2.380	-0.265, 1.755	-0.295, 1.335	-0.785, 1.685	-0.520, 1.895	-0.800, 1.555	-0.415, 1.605	-0.165, 0.415	-0.145, 0.540	-0.300, 0.875	-0.140, 0.585
Endpoint change												
n	22	19	24	12	225	96	220	114	25	13	22	19
Mean (SD)	0.09 (0.3541)	0.602 (0.5332)	0.565 (0.4894)	0.474 (0.5625)	0.042 (0.4545)	0.311 (0.3917)	0.264 (0.3768)	0.290 (0.3571)	0.010 (0.2044)	0.066 (0.2410)	0.302 (0.2631)	0.149 (0.1827)
Median	0.005	0.465	0.553	0.375	-0.005	0.240	0.218	0.238	-0.040	0.020	0.280	0.140
Min, max	-0.850, 0.840	0.085, 2.380	-0.265, 1.755	-0.295, 1.335	-1.040, 1.685	-0.520, 1.895	-0.985, 1.555	-0.415, 1.605	-0.495, 0.415	-0.335, 0.540	-0.300, 0.875	-0.140, 0.585

Source: Module 5.3.5.3, Summary 5.4

bid=twice daily; FEV_1=forced expiratory volume in 1 second; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; max=maximum; min=minimum; n=number of patients with an observation; SD=standard deviation.

2.5.2.4. Supportive study (FSS-AS-305)

Title of study:

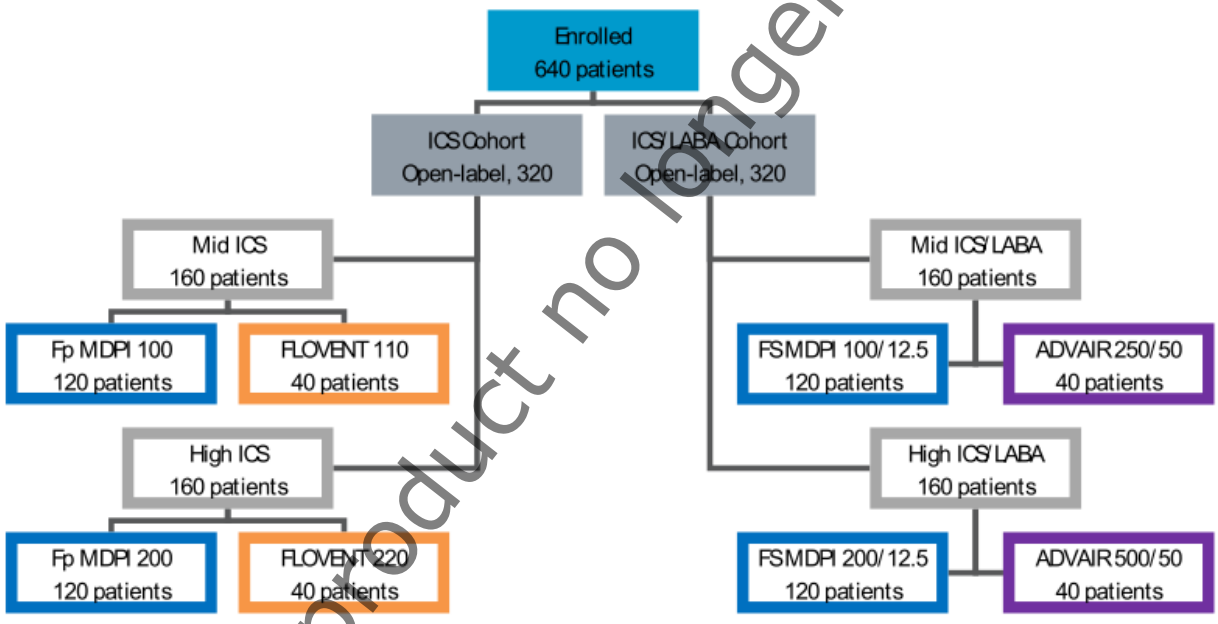
A 26-Week Open-Label Study to Assess the Long-Term Safety of Fluticasone Propionate Multidose Dry Powder Inhaler and Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler in Patients 12 Years of Age and Older with Persistent Asthma.

Methods

Study Participants

Demographic characteristics were generally well-balanced across the treatment groups and similar to the pooled and individual Phase 3 studies.

Figure 19: Overall Study FSS-AS-305 Schema



ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; FLOVENT = FLOVENT HFA; ADVAIR = ADVAIR DISKUS
Note: Numbers after drug names denote treatment strength in mcg.

Study design:

Study FSS-AS-305 was a stratified, randomised, open-label, active drug-controlled study with no blinding. The study consisted of a 14-day (±2 days) pre-treatment run-in period, during which time patients continued using their current asthma medication (except for their SABA, which was replaced by the sponsor-provided study rescue medication). This run-in period provided treatment baseline for safety and for asthma status and established compliance. After successful completion of the run-in period, patients who remained eligible were stratified by cohort (ICS or ICS/LABA) as well as by treatment strength (mid- or high-). Patients were assigned to either the ICS monotherapy cohort or the ICS/LABA-combination therapy cohort based on their current asthma maintenance therapy. Within each cohort, patients were stratified into either the mid- or high-treatment strength based on the daily dose of their current asthma maintenance therapy.

Patients in each strength of the ICS/LABA-combination cohort were randomly assigned in a 3:1 distribution to either the FS MDPI or Advair Diskus treatment group.

Run in period

During the run-in period, patients continued using their current asthma medications (i.e., ICS/LABA combination). The mid- and high-strength ICS/LABA treatment groups included only patients who were receiving an ICS/LABA combination of the same strength prior to the study and during the study run-in period. Thus, patients randomised to the mid- and high-strength FS MDPI combinations substituted FS MDPI for their existing combination inhaler. Since 286 (42.4%) patients of the overall study population were using Advair Diskus as their usual medication prior to the study, patients randomised to the mid- and high-strength Advair Diskus treatment groups were a mixed population with some substituting Advair Diskus for a different combination inhaler and some continuing to use Advair Diskus at the same strength. This run-in period provided treatment baseline for safety and for asthma status and established compliance.

Treatments

Fp MDPI, 100 and 200 mcg, 1 inhalation twice a day and FS MDPI, 100/12.5 and 200/12.5 mcg, 1 inhalation twice a day.
Flovent HFA, 110 and 220 mcg, 2 puffs twice a day; Advair Diskus, 250/50 and 500/50 mcg, 1 inhalation twice a day.
The treatment period lasted for 26 weeks.

Objectives

The primary objective of the study was to evaluate the long-term safety of Fp inhalation powder in 2 strengths and FS inhalation powder in 2 strengths when administered with the Teva MDPI device over 26 weeks in patients 12 years of age and older with persistent asthma.

The secondary objective of the study was to evaluate the safety of Fp MDPI in comparison to Flovent HFA and FS MDPI in comparison to Advair Diskus.

The efficacy objective of the study was to evaluate the efficacy of Fp MDPI in comparison to Flovent HFA and FS MDPI in comparison to Advair Diskus.

Outcomes/endpoints

The primary outcome measure was the incidence and type of all adverse events for Fp MDPI and FS MDPI.

Efficacy was not a primary or secondary objective in this study. The principal efficacy variable was the change from baseline in trough FEV1 over the 26-week treatment period.

Sample size

674 patients were randomised to receive Fp MDPI, FS MDPI, Flovent HFA, or Advair Diskus, and 673 patients received at least 1 dose of study drug and were evaluated for safety in the study.

Randomisation and Blinding (masking)

FSS-AS-305 was a randomised, open-label, active drug-controlled study with no blinding. Patients were stratified by cohort (ICS or ICS/LABA) and by treatment strength (mid- or high-). Patients were assigned to either the ICS-monotherapy cohort or the ICS/LABA combination cohort based on their current (before the SV or, if needed, the pre-screen visit) asthma maintenance therapy. Within each

cohort, patients were assigned to either the mid- or high-treatment strength based on the daily dose of their current asthma maintenance therapy. Patients in each strength of the ICS-monotherapy cohort were randomly assigned in a 3:1 distribution to either the Fp MDPI or Flovent HFA treatment arm. Patients in each strength of the ICS/LABA-combination cohort were randomly assigned in a 3:1 distribution to either the FS MDPI or Advair Diskus treatment arm. It was possible for strengths and cohorts to be closed once predetermined randomisation goals were met.

Statistical methods

The primary outcome measure was the incidence and type of all adverse events for Fp MDPI and FS MDPI.
Efficacy was not a primary or secondary objective in this study. The principal efficacy variable was the change from baseline in trough FEV1 over the 26-week treatment period. The FAS was used for all analyses of efficacy data.

Principal efficacy analysis

The principal efficacy analysis of change from baseline (collected at TV1) in trough FEV1 over the 26-week treatment period (with mid- and high-strength data combined within each cohort) was performed using a MMRM with effects due to baseline FEV1, sex, age, (pooled) investigational centre, visit, treatment, and visit-by-treatment interaction. No explicit structure was assumed for the covariance among the repeated measures. Contrasts for treatment comparisons of interest were constructed. Missing data were not explicitly imputed in the MMRM analyses, but all non-missing data for a patient were used within the analysis to estimate the time-averaged difference between treatment groups over 26 weeks. While safety was the primary objective of the study, there was reasonable power for demonstrating non-inferiority of the study drug to the comparator drug within each cohort. The statistical analysis plan specified that noninferiority would be demonstrated if the lower limit of the 95% CIs for the treatment difference was greater than –125 mL.

No sensitivity analysis of the principle analysis was planned for this study.

No efficacy subgroup analysis of the principle analysis was planned.

Analysis sets

The safety population included all randomised patients who received at least 1 dose of randomised study drug. Treatment was assigned based upon the treatment patients actually received, regardless of the treatment to which they were randomised. The safety population was used for all analyses of safety data, including safety subgroup analyses.

The intent-to-treat (ITT) population included all randomised patients. Treatment was assigned based on the treatment to which patients were randomised, regardless of which treatment they actually received.

The full analysis set (FAS) included all patients in the ITT population who received at least 1 dose of study drug and had at least 1 postbaseline trough FEV1 assessment. The FAS was used for all analyses of efficacy data.

Results

Participant flow

674 patients with persistent asthma were randomly assigned to treatment within the following treatment type and strength cohorts:

Study Participant flow

Figure 20: Patient Disposition (All Patients)

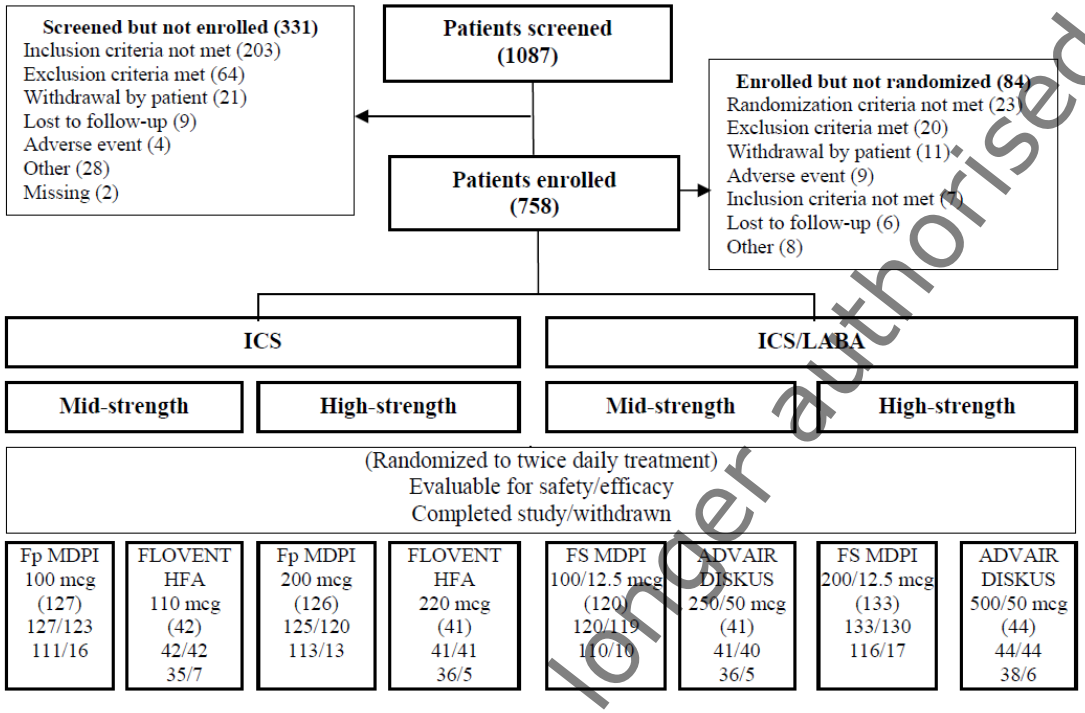


Table 26: Study Populations and Disposition by Cohort and Treatment Group (All Patients)

	ICS Cohort: Mid-strength		ICS Cohort: High-strength	
Population/Analysis Set	**Fp MDPI 100 mcg BID N = 127**	**FLOVENT HFA 110 mcg BID N = 42**	**Fp MDPI 200 mcg BID N = 126**	**FLOVENT HFA 220 mcg BID N = 41**
Intent to Treat Population, n (%)	127 (100)	42 (100)	126 (100)	41 (100)
Safety Population, n (%)	127 (100)	42 (100)	125 (>99)	41 (100)
Full Analysis Set, n (%)	123 (97)	42 (100)	120 (95)	41 (100)
Completed Study, n (%)	111 (87)	35 (83)	113 (90)	36 (88)
	ICS/LABA Cohort: Mid-strength		**ICS/LABA Cohort: High-strength**	
Population/Analysis Set	**FS MDPI 100/12.5 mcg BID N = 120**	**ADVAIR DISKUS 250/50 mcg BID N = 41**	**FS MDPI 200/12.5 mcg BID N = 133**	**ADVAIR DISKUS 500/50 mcg BID N = 44**
Intent to Treat Population, n (%)	120 (100)	41 (100)	133 (100)	44 (100)
Safety Population, n (%)	120 (100)	41 (100)	133 (100)	44 (100)
Full Analysis Set, n (%)	119 (>99)	40 (98)	130 (98)	44 (100)
Completed Study, n (%)	110 (92)	36 (88)	116 (87)	38 (86)

Demographic Characteristics

The treatment groups were similar in most demographic characteristics. However, the age of mid-strength ICS patients (mean: 41.5 years in the Fp MDPI 100 mcg group and 38.4 years in the Flovent HFA 110 mcg group; median: 41.0 and 40.0 years, respectively) appeared to be slightly lower than the ages of patients in other groups (means ranged from 42.0 to 46.1 years; medians ranged from 44.5 to 52.0 years). Most groups had a slightly larger proportion of females than males; the sexes were more equivalently represented in the Advair Diskus groups and the FS MDPI 200/12.5 mcg group. In all

treatment groups, mean BMI values (ranging from 28.6 to 32.0 kg/m2; median values were similar) indicated that the study population was mostly overweight to obese.

Recruitment

Period: 14 July 2014 to 20 July 2015

Duration of Treatment: This study consisted of a SV, a 14-day (±2 days) run-in period, a 26-week treatment period, and a 1-week follow-up period. Patients were expected to participate in this study for a minimum of 29 weeks. It was also possible for patients to participate in an optional pre-screening period for up to 30 days before the SV, during which no study drug was administered.

Conduct of the study

There was 1 amendment (dated 14 January 2015) to the protocol for this study to change when an asthma exacerbation was to be considered a serious adverse event. An asthma exacerbation, regardless of severity, was to be recorded as an adverse event only if it met the criteria of a serious adverse event. Otherwise they were to be recorded only on the asthma exacerbation page of the CRF. Before the amendment was issued, the definition of a serious adverse event mandated that any severe asthma exacerbation, defined as an event that required systemic corticosteroid use for ≥3 days or hospitalisation or an ED visit because of asthma requiring treatment with systemic corticosteroids, was required to be reported as a serious adverse event regardless of whether it met the standard criteria for serious adverse events. The amendment removed this requirement, thus instituting more standard criteria for the definition of a serious adverse event.

Baseline data

Baseline characteristics were generally similar across treatment groups. All patients enrolled in the study were required to have a diagnosis of persistent asthma. The duration of asthma history was at least 10 years for the majority of patients across treatment groups. The Fp MDPI 200 mcg group, however, was notable for having 20 (16%) patients with asthma duration of 1 to <5 years, compared with a range of 2% to 11% with this duration across other groups. Previous MDI experience was more variable across treatment groups, but most patients had MDI experience of at least 10 years. Previous DPI experience was also variable across treatment groups, but the majority had at least 1 year and less than 15 years.

Numbers analysed

These 674 patients were included in the ITT population. A total of 673 (>99%) patients received at least 1 dose of study drug and were evaluable for safety; 659 (98%) patients were evaluable for efficacy (FAS); and 595 (88%) patients completed the study (at least 26 weeks of open-label treatment).

A total of 79 (12%) patients were discontinued from the study, including 41 (12%) patients in the ICS cohort (in which the highest rate of withdrawals [7 (17%) patients] occurred in the Flovent HFA 110 mcg group and the lowest rate [13 (10%) patients] occurred in the Fp MDPI 200 mcg group) and 38 (11%) patients in the ICS/LABA cohort (in which the highest rate of withdrawals [6 (14%) patients] occurred in the Advair Diskus 500/50 mcg group and the lowest rate [10 (8%) patients] occurred in the FS MDPI 100/12.5 mcg group).
Withdrawal rates across all treatment groups ranged from 8% to 17%. The most frequent reason for withdrawal across all treatment groups was withdrawal by patient, which occurred for 37 patients overall, which was 46.8% of the 79 patients overall who withdrew and 5% of randomised patients. No treatment group had a notably greater rate of withdrawals compared with the other groups. Eleven

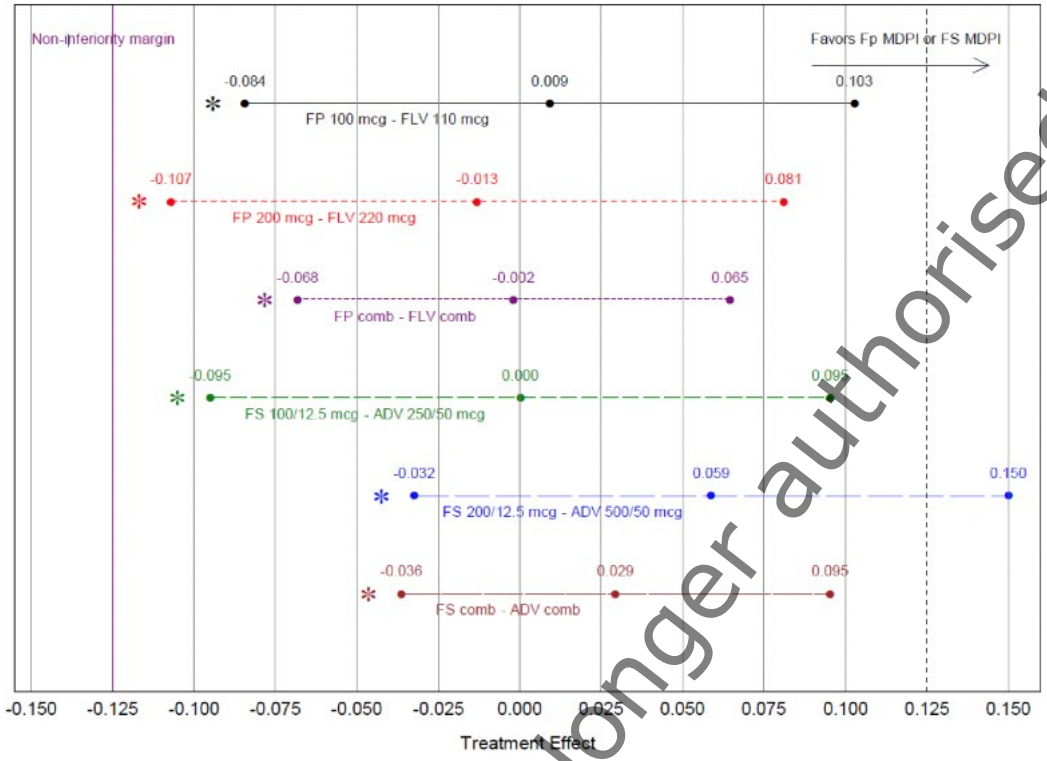
patients discontinued treatment because of adverse events. Two patients discontinued treatment because of lack of efficacy, and 2 patients discontinued treatment because of disease progression.

Outcomes and estimation

The treatment effect and the lower limit of the 95% CIs for all doses of Fp MDPI and FS MDPI exceeded the –125 mL non-inferiority margin for FEV_1 when compared to Flovent HFA and Advair Diskus, respectively For FS MDPI, numerical differences favoured FS MDPI over Advair Diskus at the high dose. The non-inferiority margin of -125 mL was below the estimated minimal clinically important difference of 230 mL reported for FEV_1. The applicant considered that the study drug was at least as effective as the comparator drug for both the ICS and ICS/LABA cohorts. While the study design was open-label due to the difficulty of blinding the active comparator, the applicant considered that the efficacy results were useful to show that meaningful differences between the treatments were not observed.

The non-inferiority comparison is displayed graphically in Figure 20. The top 3 lines represent the comparisons for the mono-product, Fp MDPI versus Flovent HFA, while the bottom 3 lines represent the comparison of FS MDPI and Advair Diskus for the mid-strength doses (3rd from bottom) followed by the comparison of the high-strength doses, with the comparison of both strengths combined at the bottom. In the case of the mid-strength comparison, the 95% CI was centred around 0, while for the high-strength dose comparison, it was shifted to the right in favour of FS MDPI over Advair Diskus. According to the applicant, the data supported the comparability of both the mid- and high-strength doses of FS MDPI to Advair Diskus. It is not thought to be reasonable to extrapolate this comparison to low-strength FS MDPI based on *in vitro* proportionality of the 3 dose strengths, the relative efficacy of the low-strength dose compared to the mid-strength dose in Study FSS-AS-301, and the demonstrated efficacy of the low-strength dose compared to placebo.

Figure 21: Trough FEV1 (L) Treatment Effect Analysis by Cohort (Full Analysis Set, Study FSS-AS-305)



Source: MAA 120 D Questions, Figure 5.
ADV=ADVAIR DISKUS; comb=combined; FEV_1=forced expiratory volume in 1 second; FLV=FLOVENT HFA; FP=fluticasone propionate; Fp MDPI=fluticasone propionate multi-dose dry powder inhaler; FS=fluticasone propionate/salmeterol xinafoate; FS MDPI=fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler; HFA=hydrofluoroalkane.
Note: The asterisk symbol indicates that non-inferiority is shown with the prespecified margin of -0.125 L.

In Study FSS-AS-305, the primary efficacy variable of the change from baseline in trough FEV1 over the 26-week treatment period was comparable for both the mid- and high-dose strengths between the FS MDPI and ADVAIR DISKUS treatments within the respective ICS/LABA dose strength cohorts (Table 27).

Table 27: Analysis of Change From Baseline in Trough FEV1 Over the 26-Week Treatment Period (ICS/LABA Cohort; Study FSS-AS-305)

ICS Cohort	Mid-strength		High-strength		High-/Mid-strength combined	
Variable Statistic	FS MDPI 100/12.5 mcg bid (N=119)	ADVAIR DISKUS 250/50 mcg bid (N=40)	FS MDPI 200/12.5 mcg bid (N=130)	ADVAIR DISKUS 500/50 mcg bid (N=44)	FS MDPI bid (N=249)	ADVAIR DISKUS bid (N=84)
Change in trough FEV_1 (L) over 26 weeks n[a]	119	40	130	44	249	84
LS mean	0.116	0.117	0.100	0.041	0.108	0.079
SE of LS mean	0.0251	0.0419	0.0235	0.0399	0.0173	0.0290
95% CI	(0.067,0.166)	(0.034, 0.199)	(0.054,0.146)	(-0.037,0.119)	(0.074,0.142)	(0.022,0.136)
Comparison to ADVAIR DISKUS (FS MDPI – ADVAIR DISKUS)						
Difference of LS mean	0.000		0.059		0.029	
SE of LS mean	0.0485		0.0464		0.0335	
95% CI	(-0.095,0.095)		(-0.032,0.150)		(-0.036,0.095)	
p-value	0.9966		0.2056		0.3821	

Source: CSR FSS-AS-305 Table 23 (Summary 15.2.1.1 and Listing 16.2.6.1).
[a] Denotes the number of patients who contribute at least once to the analysis
bid=twice daily; CI=confidence interval; CSR=clinical study report; FAS=full analysis set; FEV_1=forced expiratory volume in 1 second; FS MDPI=fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; ICS=inhaled corticosteroid; LS=least squares; LABA=long-acting β_2-agonist; MMRM=mixed model for repeated measures; N=number of patients; SE=standard error.
Notes: The analysis is based on an MMRM with adjustment for baseline FEV_1, sex, age, (pooled) investigational centre, visit, treatment, and treatment-by-visit. An unstructured covariance matrix is used in the MMRM model.

2.5.3. Discussion on clinical efficacy

Dose response studies

The study design, subject disposition and recruitment criteria were appropriate in the studies submitted in support of dose selection for the monotherapy components of BroPair Spiromax. The studied population were relevant to the enrolled population in pivotal studies and the efficacy endpoints (trough FEV_1) were considered clinically relevant.

The 3 doses of fluticasone propionate (Fp) were selected for Phase 3 development on the basis of PK studies along with efficacy and safety in Phase 2 dose-ranging studies (FpS-AS-201 and FpS-AS-202). The assessment of Fp PK parameters in the Phase 2 studies demonstrated proportional increases in the PK parameters across all the doses tested. The Fp doses selected (50, 100, and 200 mcg) were shown to be the most effective doses in the treatment of patients with asthma that were symptomatic despite ICS therapy. Similarly, the salmeterol dose for Phase 3 development was selected on the basis of PK studies along with efficacy and safety in a Phase 2 dose-ranging study (FSS-AS-201). Increased systemic exposure to salmeterol with increasing FS MDPI doses, dose-related improvements in pulmonary function, and a similar benefit provided by the FS MDPI 100/12.5 mcg dose relative to Advair Diskus 100/50 mcg all supported the selection of the 12.5 mcg dose of salmeterol for Phase 3 development.

However, the proposed doses contain significantly lower amounts of the active substances compared to the extensively studied and already marketed combination of Fp and salmeterol. Therefore, the applicant was requested by CHMP to justify the amount of salmeterol, which is considered very low compared to the amount in the already marketed products, with established efficacy/safety and with at least 20 years post-marketing experience. The use of 30-minute partial exposure data has been recognised as a mean to assess the efficacy of medicinal products, such as salmeterol, that are characterised by very rapid lung absorption and significant but delayed gastrointestinal absorption. Using this approach, the early exposure (AUC0-30min ratio) in the clinical studies comparing FS MDPI

and Advair Diskus resulted in exposure ratios of 0.766 and 0.848, which could support that delivery to the lungs is not substantially less. This is further discussed in section 2.4.4 'Discussion on clinical pharmacology' and was acknowledged by CHMP. In addition, the clinical data demonstrated a dose response for efficacy using a range of salmeterol doses tested in the Phase 2 Study FSS-AS-201 that were specifically designed to select the most optimal dose of salmeterol. The applicant stated that the dose of salmeterol selected for FS MDPI for Phase 3 development, 12.5 mcg, was based on indications of therapeutic comparability to salmeterol 50 mcg in the active comparator, Advair Diskus in the Phase 2 study. The Applicant therefore considered that the Phase 2 salmeterol dose-ranging study efficacy data with the active comparator Advair Diskus, the PK exposure data, and the Phase 3 clinical efficacy data indicated that the formulation strategy was successful for salmeterol in achieving comparable efficacy with a lower dose strength.

Moreover, there were no robust dose response relation based on the phase II studies with Fp monotherapy and CHMP considered that the design of the studies might not have been optimal to detect differences between the three different strengths. Therefore, the applicant was requested to provide further justification on the Fp doses chosen and to further discuss any additional benefit with the increase in Fp strength. The applicant highlighted that dose-ranging studies that had been conducted with the Fp mono-product did not report statistically significant differences between Fp doses but, in general, reported tendencies for dose-related improvements. The applicant provided the results of 3 studies from the Literature characterizing the change in FEV_1 in response to different doses of Fp. A comparison of 100 mcg/day and 200 mcg/day doses of Fp resulted in a difference of approximately 40 mL in the change from baseline in FEV_1 at endpoint. For comparison, in Study FSS-AS-301 submitted in this application, the difference in the FEV_1 change from baseline between the Fp MDPI 100 mcg/day (mid ICS dose) and 200 mcg/day (high ICS dose) treatment groups was approximately 32 mL, and in Study FSS-AS-30017 submitted in this application, the difference was approximately 60 mL between the Fp MDPI 200 mcg/day and 400 mcg/day treatment groups. According to the applicant, in order to see bigger differences, it is necessary to use doses of Fp that differ by more than 2-fold. Overall, CHMP acknowledged the applicant's position on the relatively flat dose-response curve to Fp and ICSs in general which is well described and supported by the literature. CHMP also agreed that the benefit of combining an ICS with a LABA compared to an ICS alone has been demonstrated throughout the literature, whether the combination is compared to the same ICS dose or an increased ICS dose. It was acknowledged that due to the small differences in efficacy between Fp doses, a detectable difference in lung function between doses of the combination is not expected because the addition of salmeterol is likely to obscure any small difference. Nevertheless, while the applicant presented sufficient justification for the salmeterol dose and the three doses of Fp based on Phase 2 studies, the low FS MDPI dose strength was considered to be insufficiently supported by the clinical efficacy Phase 3 results. This is further discussed below.

Main studies

Design and conduct of clinical studies

Two replicate, placebo-controlled, randomised, parallel-group, 12-week Phase 3 efficacy and safety studies (FSS-AS-301 and FSS-AS-30017) in adult and adolescent patients (12 years of age or older) with asthma were conducted to evaluate the efficacy of FS MDPI across a spectrum of asthma severities. In addition to these studies, a 26-week, open-label, long-term safety and efficacy study with the mid- and high-strength doses of FS MDPI was conducted (Study FSS-AS-305).

Studies FSS-AS-301 and FSS-AS-30017 were designed to show superiority of Fp mono-product (nominal doses of 50, 100, and 200 mcg) over placebo and to show superiority of the FS combination (nominal doses of 50/12.5, 100/12.5, and 200/12.5 mcg) over Fp mono-product in adults and

adolescents in a broad range of asthma severity. The primary endpoints in both studies were the change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) FEV_1 at week 12 and the standardised baseline-adjusted post-dose FEV1 AUEC0-12h at the week 12 visit, analysed for the subset of approximately 300 patients who performed post-dose serial spirometry.

Deviations from the Guideline on the clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1) in treatment duration (12 weeks instead of at least 6 months) and primary endpoint (lung function instead of reduction in asthma exacerbations) are considered to be acceptable based on the well- recognised efficacy of fluticasone and salmeterol. With regard to the long-term safety study (FSS-AS-305), considering the well-recognised efficacy and safety of fluticasone and salmeterol a six months safety study was considered to be adequate to assess the safety of BroPair Spiromax.

It is, however, noted that the initially intended indication for the FS MDPI combination product also contains a substitution indication [patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist]. This substitution indication would include the switch from an open combination of any ICS and any LABA but also the switch from any LABA/ICS fixed combination products. Whereas the step-up indication [patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 agonist] could be considered well covered by the clinical programme (EMEA/H/SA/3754/1/2018/II), the substitution indication was not (this is further discussed below).

The inclusion and exclusion criteria in the Phase 3 studies were the same with those commonly used in asthma studies and thus considered acceptable. Inclusion and exclusion criteria were designed to allow for selection of patients with well-characterised asthma that was stable enough for the study and were likely to benefit from treatment with FS MDPI. Since the dose of ICS was used to define patients' asthma severity, different baseline asthma therapies were required for inclusion in the studies reflecting the dose of ICS being studied. This ensured that a range of asthma severity was evaluated in the development programme to treat a broadened spectrum of asthma severity encountered clinically.

The randomisation criteria and schemes as well as blinding were considered acceptable.

Most of the major amendments for Studies FSS-AS-301 and Study FSS-AS-30017 were made to the protocol, based on regulatory feedback or at the request of regulatory authorities. However, those are not considered to have an impact on the outcome of the study.

The primary endpoint 'change in FEV_1 at week 12' can be considered adequate since the effect of ICS can be assessed after 3 months. Furthermore, this primary endpoint can be considered acceptable as a commonly used endpoint for respiratory products intended for use in asthmatic patients. Upon request by CHMP, the applicant clarified why the comparison of FS MDPI vs Fp MDPI for trough FEV_1 was not included in the primary endpoint. A sequential approach was used in the study design, first comparing the mono-product to placebo to demonstrate a significant effect, and then comparing the combination to the mono-product, to prove the efficacy of Fp MDPI and the FS MPDI combination. Moreover, two different endpoints were used to demonstrate efficacy of inhaled corticosteroids and long-acting β2-agonists, which act by different mechanisms to improve pulmonary function.

Efficacy data and additional analyses

FSS-AS-301 and FSS-AS-30017

In the 2 pivotal Phase 3 studies (FSS-AS-301 and FS-AS-30017), 1375 patients were randomised to Fp MDPI, FS MDPI, or placebo treatment; and of those patients, 1360 were included in the FAS

population. The majority of patients in all treatment groups in the FAS population completed the study; only 9% of patients overall withdrew from the studies prematurely.

Patients were required to be on a stable maintenance dose of low- or mid-strength ICS or ICS/LABA (Study FSS-AS-301) or mid- to high-strength ICS or ICS/LABA (Study FSS-AS-30017) at study entry. Study FSS-AS-301 evaluated low- to mid-doses of Fp MDPI 50 and 100 mcg bid and FS MDPI 50/12.5 and 100/12.5 mcg bid, whereas Study FSS-AS-30017 evaluated mid to high doses of Fp MDPI 100 and 200 mcg bid and FS MDPI 100/12.5 and 200/12.5 mcg bid.

In both studies the primary endpoints included:

1. Change from baseline in trough (AM pre-dose and pre-rescue bronchodilator) FEV_1 at week 12
2. Standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12, analysed for the subset of approximately 300 patients who performed serial spirometry

A fixed-sequence multiple testing procedure was used to control the overall Type I error rate at the 0.05 level (2-sided) for the primary endpoints analysis.

Phase 3 Studies Efficacy Results

In both studies, the results for the change from baseline in trough FEV_1 at week 12 in the Fp MDPI and FS MDPI groups were statistically significantly superior to those in the placebo group.

Comparisons of combination therapy with monotherapy were not controlled for multiplicity but indicated improvement for FS MDPI 50/12.5 mcg compared with Fp MDPI 50 mcg (p=0.0022) and Fp MDPI 100 mcg (p=0.0166) and for FS MDPI 100/12.5 mcg compared with Fp MDPI 100 mcg (p=0.0202) in Study FSS-AS-301 and improvement for FS MDPI 100/12.5 mcg compared with Fp MDPI 100 mcg (p=0.0005) and Fp MDPI 200 mcg (p=0.0356) and for FS MDPI 200/12.5 mcg compared with Fp MDPI 200 mcg (p=0.0309) in Study FSS-AS-30017.

Results for the standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ based on serial spirometry for combination therapy compared with monotherapy indicated that FS MDPI 100/12.5 mcg and 200/12.5 mcg doses were statistically significantly superior to Fp MDPI 100 and 200 mcg doses, respectively, and that FS MDPI 50/12.5 and 100/12.5 mcg doses were statistically significantly superior to Fp MDPI 50 and 100 mcg doses, respectively. There were also improvements for FS MDPI 50/12.5 and 100/12.5 mcg doses compared with Fp MDPI 100 and 200 mcg doses, respectively. Results for the standardised baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ based on serial spirometry in the FS MDPI and Fp MDPI groups were statistically significantly superior to those in the placebo group.

In both studies combined, all dose strengths of the FS MDPI combination compared to placebo for trough FEV_1 resulted in a difference from placebo in least squares (LS) mean ranging from 0.262 to 0.276 L (all p-values for comparisons were <0.0001). In comparing the Fp MDPI mono-product doses, there were numeric differences between the doses in trough FEV_1 ranging from approximately 30 to 60 mL. According to the applicant, this is consistent with the flat dose-response curve that is consistently reported for all ICS and the reported differences for Fp in the literature. The trough FEV_1 endpoint is not expected to be able to differentiate between different doses of the combination due to the relatively small dose response to Fp and the confounding influence of the added LABA.

For all dose strengths of the FS MDPI combination compared with placebo for the post-dose FEV_1 $AUEC_{0\text{-}12h}$, the difference in LS mean from placebo ranged from 0.322 to 0.335 L (all p- values for comparisons were <0.0001). This endpoint primarily assesses bronchodilation due to the LABA salmeterol. Since all strengths of the combination used the same dose of salmeterol, it was considered that this endpoint is not expected to differentiate between the combination doses.

Overall, the data provided showed for both primary endpoints superiority for Fp MDPI over placebo and superiority for the FS MDPI combination over Fp MDPI. These findings are expected based on the well-known efficacy pattern for the fluticasone propionate and salmeterol substances. However, CHMP considered that the recorded differences between doses investigated were minor and the clinical relevance questionable. While this could be expected as the dose/effect relationship is known to be flat and thus assay sensitivity for picking up differences between doses often poor with this kind of study design, CHMP expressed some concerns about the clinical efficacy results of the FS MDPI low dose obtained in FSS-AS-301 (this is further discussed below).

Pooled data from Studies FSS-AS-301 and FSS-AS-30017

In the pooled Phase 3 studies, the demographics characteristics were similar across the FS MDPI and placebo treatment groups.

Pooled data from Studies FSS-AS-301 and FSS-AS-30017 by dose group showed similar baseline trough FEV_1 values across all FS MDPI and placebo groups. At week 12, all FS MDPI dose groups showed greater increases in mean change trough FEV_1 (0.340, 0.300, and 0.290 L in the 50/12.5, 100/12.5, and 200/12.5 mcg groups, respectively) than the placebo group (0.104 L). At week 12, the increase in mean baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ was similar (0.366, 0.356, and 0.369 L) in the FS MDPI 50/12.5, 100/12.5, and 200/12.5 mcg groups, respectively. All FS MDPI dose groups showed greater increases in mean baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ than the corresponding Fp MDPI groups (0.212, 0.192, and 0.194 L in the 50, 100, and 200 mcg groups, respectively) and the placebo group (0.032 L).

Primary efficacy results presented for each of the three proposed strengths (low, mid and high)

Low-strength Combination (FS MDPI 50/12.5 mcg)

The low-strength combination was assessed in Study FSS-AS-301.

The change from baseline in trough FEV_1 was 0.319 L for the FS MDPI low-strength combination compared with 0.053 L for placebo and 0.172 L for Fp MDPI 50 mcg. When FS MDPI 50/12.5 mcg was compared to placebo, the difference was 0.266 L ($p<0.0001$), and when compared to Fp MDPI 50 mcg, the difference was 0.147 L ($p=0.0022$).

The change from baseline post-dose FEV1 AUC0-12h was 0.399 L for the FS MDPI low-strength combination (50/12.5 mcg) compared to 0.074 L for placebo and 0.268 L for Fp MDPI 50 mcg. When FS MDPI 50/12.5 mcg was compared to placebo, the difference was 0.325 L ($p=0.0000$) and when compared to Fp MDPI 50 mcg, the difference was 0.131 L ($p=0.0322$). The difference between the low-strength FS MDPI and Fp MDPI provides evidence for the added benefit of salmeterol in the low-strength dose.

Mid-strength Combination (FS MDPI 100/12.5 mcg)

The mid-strength combination was assessed in patients with both mild to moderate asthma (Study FSS-AS-301) and moderate to severe asthma (Study FSS-AS-30017).

In patients with mild to moderate asthma, the change from baseline in trough FEV_1 was 0.315 L for the FS MDPI mid-strength combination compared to 0.053 L for placebo and 0.204 L for Fp MDPI 100 mcg. When FS MDPI 100/12.5 mcg was compared to placebo, the difference was 0.262 L ($p<0.0001$), and when compared to Fp MDPI 100 mcg, the difference was 0.111 L ($p=0.0202$).

In patients with moderate to severe asthma, the change from baseline in trough FEV_1 was 0.271 L for the FS MDPI mid-strength combination compared to -0.004 L for placebo and 0.119 L for Fp MDPI 100 mcg. When FS MDPI 100/12.5 mcg was compared to placebo, the difference was 0.274 L ($p<0.0001$),

and when compared to Fp MDPI 100 mcg, the difference was 0.152 L (p=0.0005). Thus, in both patient populations, the FS MDPI 100/12.5 mcg showed significant improvement in trough FEV_1 over placebo and over Fp MDPI 100 mcg.

These observations were however considered to be predictable since the dose is the same, the inhaler is the same and only the addition of salmeterol can produce some difference.

In patients with mild to moderate asthma, the change from baseline post-dose FEV1 AUC0-12h was 0.408 L for the FS MDPI mid-strength combination compared to 0.074 L for placebo and 0.254 L for Fp MDPI 100 mcg When FS MDPI 100/12.5 mcg was compared to placebo, the difference was 0.335 L (p=0.0000), and when compared to Fp MDPI 100 mcg, the difference was 0.154 L (p=0.0076).

In patients with moderate to severe asthma, the change from baseline post-dose FEV1 AUC0-12h was 0.442 L for the FS MDPI mid-strength combination compared to 0.121 L for placebo and 0.260 L for Fp MDPI 100 mcg. When FS MDPI 100/12.5 mcg was compared to placebo, the difference was 0.322 L (p=0.0000), and when compared to Fp MDPI 100 mcg, the difference was 0.182 L (p=0.0010).

Thus, in both populations, the difference between the mid-strength FS MDPI (100/12.5 mcg) and Fp MDPI 100 mcg provides evidence for the significant added benefit of salmeterol in the mid strength dose.

High-strength Combination (FS MDPI 200/12.5 mcg)

The change from baseline in trough FEV_1 was 0.272 L for the FS MDPI high-strength combination compared to -0.004 L for placebo and 0.179 L for Fp MDPI 200 mcg. When FS MDPI 200/12.5 mcg was compared to placebo, the difference was 0.276 L (p-value<0.0001), and when compared to Fp MDPI 200 mcg, the difference was 0.093 L (p=0.0309). The difference between FS MDPI and Fp MDPI for the trough FEV_1 endpoint reflects the contribution of salmeterol at the end of the dosing period.

The change from baseline post-dose FEV1 AUC0-12h was 0.446 L for the FS MDPI high-strength combination compared to 0.121 L for placebo and 0.267 L for Fp MDPI 200 mcg. When FS MDPI 200/12.5 mcg was compared to placebo, the difference was 0.326 L (p=0.0000), and when compared to Fp MDPI 200 mcg, the difference was 0.179 L (p=0.0009). The difference between the high-strength FS MDPI and Fp MDPI provides evidence for the significant added benefit of salmeterol in the high-strength combination.

Supportive Phase 3 Study FSS-AS-305

This was a 26-week, randomised, open-label, active drug-controlled, Phase 3 study in 674 patients with persistent asthma. Patients were stratified by cohort (ICS or ICS/LABA) and by treatment strength (mid or high). Patients were randomly assigned in a 3:1 distribution (investigational drug: comparator) based on their prior asthma maintenance therapy to either open-label Fp MDPI (100 or 200 mcg) or Flovent HFA (110 or 220 mcg) (ICS cohort) or FS MDPI (100/12.5 or 200/12.5 mcg) or Advair Diskus (250/50 or 500/50 mcg) (ICS/LABA cohort). Within each cohort, patients were assigned to either the mid- or high-strength treatment based on the daily dose of their current asthma maintenance therapy.

Demographic characteristics were generally well-balanced across the treatment groups and similar to the pooled and individual Phase 3 studies.

While safety was its primary objective, the study included a planned efficacy analysis of the change from baseline in trough FEV_1 over the 26-week treatment period. The applicant considered that this had reasonable power for demonstrating non-inferiority of the investigational product to the comparator product within each cohort.

The non-inferiority comparison, in an open label setting, of the mid- and high-strength doses of the combination showed that FS MDPI was non-inferior to Advair Diskus (lower limit of non-inferiority of -0.125 L). In direct comparison of FS MDPI (200/12.5 mcg) to Advair Diskus (500/50 mcg), the LS mean difference was 0.059 (95% CI: -0.032, 0.150). The high-strength dose of FS MDPI (200/12.5 mcg) is according to the applicant comparable to the high-strength dose of Advair Diskus (500/50 mcg). This, however, was performed with an open-label study design and thus the results are questionable. In addition, there was no direct demonstration of therapeutic equivalency or comparable efficacy of FS MDPI (200/12.5 mcg) to Advair Diskus (500/50 mcg). Therefore, serious concerns were expressed by CHMP with regard to the initially proposed substitution indication. This is further discussed below.

Elderly (patients >65 years of age)

The data submitted for patients older than 65 years of age were considered to be limited by CHMP. Furthermore, there was a greater variability in the treatment responses observed in the >65 years of age subgroup. Upon request by CHMP, the applicant provided further justification demonstrating that the older population did not respond differently to FS MDPI than the population as a whole. It was also agreed by CHMP that the greater variability in the treatment responses observed in the >65 years of age subgroup in this clinical programme can be attributed to the variation in a single response associated with a small sample size and not a unique characteristic of the population. Furthermore, currently approved inhaled corticosteroids and inhaled corticosteroid/long-acting β2-agonist combinations do not require any dosage adjustment for patients aged 65 years and older. Thus, the information reflected in section 4.2 of the SmPC, 'there is no need to adjust the dose in elderly patients' is supported by CHMP.

Adolescents (12 years of age and older)

Results in adolescents were consistent with those in adults in both pivotal replicate phase 3 studies. Greater effects relative to placebo were observed for FS MDPI in adolescent patients consistent with the overall treatment results observed. The combination showed a greater effect than Fp alone.

Therapeutic indication

With regard to the therapeutic indication for BroPair Spiromax, the following indication was initially proposed by the applicant:

BroPair Spiromax is indicated for use in adults and adolescents 12 years and older.

BroPair Spiromax is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting β_2 agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 agonist.

In line with the CHMP SA advice received (EMEA/H/SA/3754/1/2018/II), the CHMP considered that the second part of the indication: 'patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 agonist' (substitution indication) was not adequately supported by the clinical development programme. Furthermore, CHMP considered that therapeutic equivalence has not been adequately demonstrated between FS MDPI and the active comparator Advair Diskus in clinical study FSS-AS-305 as this study was not considered sensitive enough to demonstrate comparability of pre-dose FEV_1 between FS MDPI and Advair Diskus as there was no difference in effect between the two

ICS doses investigated. Therefore, interchangeability between FS MDPI and the approved comparator Advair Diskus (or other approved products) cannot be claimed. Therefore, a major objection was raised by CHMP. Nevertheless, within their responses, the applicant indicated that the substitution indication was not further pursued.

Moreover, CHMP considered that it was important to stress that the doses to be used with BroPair Spiromax do not correspond to any approved doses for other salmeterol/fluticasone propionate containing products. Thus, the following text was added to section 4.2 of the SmPC to avoid any potential confusion and/or dosing errors:

'Note that the delivered doses for BroPair Spiromax are different from other salmeterol/fluticasone propionate containing products on the market. The products are thus not interchangeable on dose bases and different dose levels (including medium/high doses of fluticasone propionate) for different products do not necessarily correspond to each other.'

With regard to the 'step-up' indication (patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 agonist), CHMP noted that the asthma guideline requires equal emphasis to be placed on lung function and symptomatic endpoints to provide sufficient evidence of efficacy. However, in both pivotal clinical studies 301 and 30017 and in particular in study 301 a clinically relevant patient-derived benefit as measured by AQLQ of the FS MDPI over the monotherapy Fp was not seen. Therefore, the applicant was requested by CHMP to provide further justification to support the clinical efficacy supporting the use of FS MDPI low-, mid- and high-dose strengths in the asthma 'step-up' indication.

Taking into account that fluticasone propionate (Fp) and salmeterol are not new active substances but are well-established pharmaceutical agents, primary endpoints focusing on lung function were selected accordingly by the applicant, in line with other approved ICSs and LABA inhaler development programs. This was well acknowledged by CHMP. However, the symptomatic asthma endpoints were included in secondary pre-specified analyses, and thus were not adequately powered to show a statistically significant effect. The Applicant argued that as symptomatic asthma endpoints have a high degree of variability; the BroPair Spiromax Phase 2 and Phase 3 studies were powered for their coprimary endpoints and did not have sufficient power to show significant effect for all 3 dose strengths for a single, prespecified, key secondary endpoint. Nevertheless, the applicant stated in their response that the results of pivotal studies demonstrated nominally significant improvements across a series of pre-specified symptomatic endpoints and better characterised efficacy of BroPair Spiromax in its totality across several unique symptomatic endpoints as summarised below.

Low strength: FS MDPI 50/12.5 mcg compared to Fp MDPI 50 mcg

The low-strength combination did not show a statistically significant improvement over the low-strength mono-product for any of the symptom-related endpoints in Study FSS-AS-301. However, the applicant indicated that there was a large difference between the treatments in the daily rescue medication use. The change from baseline in the weekly average daily rescue medication use over 12 weeks decreased by a greater extent with FS MDPI 50/12.5 mcg compared to Fp MDPI 50 mcg (difference of least squares [LS] mean: -0.239 puffs/day; nominal p=0.0640). In addition to a large difference in rescue medication use, there was a numeric improvement for the combination product over the mono-product across multiple symptom-related endpoints. For all the following symptom-related endpoints, the numeric difference favoured low strength of FS MDPI in providing greater benefit than the low strength of Fp MDPI.

In light of this, the applicant stated that the benefit that was seen in the reduced use of daily rescue medication together with the numeric benefits seen with the combination over the mono-product for multiple symptom-related endpoints, supports the clinical efficacy of the low-strength combination.

While several different symptom-related endpoints favoured FS MDPI, the differences between the low-strength combination treatment and the low-strength monotherapy were considered to be small by CHMP. While a clinical benefit was seen, the significance of such finding did not reach statistically significant levels.

Medium strength: FS MDPI 100/12.5 mcg compared to Fp MDPI 100 mcg

The mid-strength combination demonstrated a significant improvement over the mid-strength mono-product for the AQLQ, as well as for daily rescue medication use and the percentage of asthma control days.

Other secondary endpoints achieved large differences but did not reach statistical significance, with FS MDPI providing greater benefit than Fp MDPI for the change from baseline in both the weekly average of the daily asthma symptom score over 12 weeks (Study FSS-AS- 30017) and the percentage of rescue-free days during 12 weeks (Study FSS-AS-301). Thus, the applicant concluded that these endpoints supported the efficacy of the mid-strength combination, FS MDPI 100/12.5 mcg, in providing a significant improvement in symptom-related endpoints. This was agreed by CHMP.

High strength: FS MDPI 200/12.5 mcg compared to Fp MDPI 200 mcg

The high-strength combination demonstrated a significant improvement over the high-strength mono-product for the 3-following symptom-related endpoints the change from baseline in the weekly average of the daily asthma symptom score, the weekly average of daily rescue medication use, and the percentage of symptom-free days.

While the high-strength dose did not produce a statistically significant benefit of the combination over the mono-product for the AQLQ, the applicant indicated that this could be the result of the fact that Study FSS- AS-30017 was not powered to demonstrate a significant effect for this comparison. Overall, the endpoints of daily asthma symptom score, daily rescue medication use, and the percentage of symptom-free days support the efficacy of the high-strength combination, FS MDPI 200/12.5 mcg, in providing a significant improvement in symptom-related endpoints.

Cumulatively, the applicant was of the opinion that there was evidence of benefit for all 3 dose strengths in improving symptom- related endpoints despite the fact that statistical significance was not reached in several endpoints.

Nevertheless, CHMP considered that the available results for the proposed FS MDPI low-strength combination (FS MDPI 50/12.5 mcg) were not compelling and did not fulfil the requirements of the clinical investigation for treatment in Asthma (CHMP/EWP/2922/01 Rev.1) nor the fixed dose guideline(EMA/CHMP/158268/2017) based on the following issues: positive results on lung function alone were considered to be insufficient for approval; the low-strength combination did not show a statistically significant improvement over the low-strength mono-product for any of the symptom-related endpoints in Study FSS-AS-301 and thus a clear benefit for symptoms or asthma control was not considered to be shown. Therefore, CHMP considered that the proposed low-strength combination was not sufficiently supported by the clinical efficacy data submitted. Based on the concerns expressed by CHMP, the applicant decided to withdraw the low-strength combination for BroPair Spiromax.

Overall, CHMP considered that a favourable clinical effect was demonstrated only for the mid- and high-strength combination (FS MDPI 100/12.5 mcg and FS MDPI 200/12.5 mcg, respectively) in the Asthma 'step-up' indication.

The final indication granted by CHMP is as follows:

BroPair Spiromax is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonists.

2.5.4. Conclusions on the clinical efficacy

Overall, CHMP considered that a favourable clinical effect was demonstrated for the mid- and high-strengths of BroPair Spiromax (FS MDPI 100/12.5 mcg and FS MDPI 200/12.5 mcg, respectively) in the regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonists. The low-strength of BroPair Spiromax (FS MDPI 50/12.5 mcg) was not considered approvable and was thus withdrawn by the applicant.

2.6. Clinical safety

Introduction

A total of 9 clinical studies in adult and adolescent patients have been completed and support the safety of FS MDPI. The **Phase 3 Safety Pool** (Studies FSS-AS-301 and FSS-AS-30017) served as the primary dataset for presentation and discussion of the safety profile of FS MDPI. Additionally, results from the **Phase 2/3 Safety Pool** (Studies FSS-AS-301, FSS-AS-30017, FpS-AS-201, and FpS-AS-202), a 26-week, open-label, **long-term safety study** (Study FSS-AS-305), and the other Phase 1 and 2 studies (FSS-AS-201, FpS-AS-101, FpS-AS-102, and FSS-AS-10042) are presented where relevant as supportive information for safety assessment.

Patient exposure

In the **Phase 3 Safety Pool**, 1364 patients received at least 1 dose of study drug and were included in the safety population. Overall, 1252 patients (91%) completed 12 weeks of treatment. In the 12-week studies, 542 patients received treatment with FS MDPI.

In the **Phase 2/3 Safety Pool**, 2625 patients received at least 1 dose of study drug and were included in the safety population, and 2194 (83%) completed the study. Of the 2625 patients who received at least 1 dose of study drug, 1511 (58%) patients were in the US and 1114 (42%) patients were in other geographic regions. Of the 2625 patients in the Phase 2/3 Safety Pool, 653 (25%) patients were from the EU, while within the non-US region, 59% (653) patients were from the EU. There was a total of 1375 patients in the Phase 3 Safety Pool, and of these, 27% (365) patients were from the EU, while within the non-US region, 62% (365) patients were from the EU.

In the 26-week safety study (**Study FSS-AS-305**), a total of 673 patients received at least 1 dose of study drug and 595 patients (88%) completed 26 weeks of treatment.

In the **pooled Phase 3 studies**, the median duration of exposure in the FS MDPI dose groups was 85 days. The mean duration of exposure across all FS MDPI doses combined was 83.0 days, while in the placebo group it was slightly lower at 74.8 days because of the higher rate of premature withdrawal. This difference needs to be considered in the interpretation of the adverse events results. The majority of patients received >8 to ≤12 weeks of treatment (94% in the combined FS MDPI group and 80% in the placebo group).

In Study **FSS-AS-305**, exposure of study drug was comparable across treatment groups. The median duration of exposure was 182 days (26 weeks) in all treatment groups, and the majority of patients received treatment for between 22 and 26 weeks.

Overall Extent of exposure

The number of patients and healthy volunteers treated in each of the individual studies with FS MDPI is summarised in Table 28. A total of 3455 patients and healthy volunteers received at least 1 dose of study drug in the studies, of whom 904 received treatment with FS MDPI, all of whom received the doses proposed for commercialisation (FS MDPI 50/12.5, 100/12.5, and 200/12.5 mcg). A total of 2637 patients were randomly assigned to the 12-week studies FSS-AS-301, FSS-AS-30017, FpS-AS-201, and FpS-AS-202, and 2625 received at least 1 dose of randomised treatment. Of these, 2194 patients completed 12 weeks of treatment, of whom 519 patients received treatment with FS MDPI. In the 12-week studies, 542 patients received treatment with FS MDPI; all of whom received the doses proposed for commercialisation. A total of 674 patients were randomly assigned to the 26-week study (FSS-AS-305). Overall, 595 patients completed 26 weeks of treatment, of whom 226 patients received treatment with FS MDPI (FSS-AS-305).

Table 28: (Summary of Clinical Safety): Number of Patients and Healthy Volunteers Who Received At Least One Dose of Randomised Study Treatment in the Clinical Studies (Safety Analysis Set)

	Number of patients/healthy volunteers																					
	Placebo (bid)	Fp MDPI (mcg bid)							FS MDPI (mcg bid)						FLUTIDE DISKUS (mcg)	FLOVENT DISKUS (mcg bid)		FLOVENT HFA (mcg)		ADVAIR DISKUS (mcg bid)			Total
Study		12.5	25	50	100	200	400	100/ 6.25	50/ 12.5	100/ 12.5	200/ 12.5	100/ 25	100/ 50	100	100	250	110	220	100/ 50	250/ 50	500/ 50	
Phase 3 Safety Pool and/or Phase 2/3 Safety Pool (12-week, double-blind, placebo-controlled)																						
FSS-AS-301	129	-	-	129	129	-	-	-	128	126	-	-	-	-	-	-	-	-	-	-	-	**641**
FSS-AS-30017	144	-	-	-	145	146	-	-	-	143	145	-	-	-	-	-	-	-	-	-	-	**723**
FpS-AS-201	104	103	104	104	103	-	-	-	-	-	-	-	-	-	104	-	-	-	-	-	-	**622**
FpS-AS-202	106	-	-	107	107	106	107	-	-	-	-	-	-	-	-	106	-	-	-	-	-	**639**
Subtotal	483	103	104	340	484	252	107	-	128	269	145	-	-	-	104	106	-	-	-	-	-	**2625**
Long-term safety study (26-week, open-label)																						
FSS-AS-305	-	-	-	-	127	125	-	-	-	120	133	-	-	-	-	-	42[a]	41[a]	-	41	44	**673**
Supportive safety studies (single-dose, crossover)																						
FSS-AS-201	-	-	-	-	67[b]	-	-	68[b]	-	69[b]	-	67[b]	68[b]	-	-	-	-	-	66[b]	-	-	**69[c]**
FpS-AS-101	-	-	-	-	-	-	17[d]	-	-	-	-	-	-	-	-	18[e]	-	18[e]	-	-	-	**18[c]**
FpS-AS-102	-	-	-	-	30[e]	30[e]	-	-	-	-	-	-	-	30[e]	-	-	-	-	-	-	-	**30[c]**
FSS-AS-10042	-	-	-	-	-	40[b]	-	-	-	-	40[b]	-	-	-	-	40[d]	-	-	-	-	40[b]	**40[c]**
Subtotal	-	-	-	-	97	70	17	68	-	69	40	67	68	30	-	58	-	18	66	-	40	**157**
Total	**483**	**103**	**104**	**340**	**708**	**447**	**124**	**68**	**128**	**458**	**318**	**67**	**68**	**30**	**104**	**164**	**42**	**59**	**66**	**41**	**84**	**3455**

Source: FSS-AS-301 CSR, Section 10; FSS-AS-30017 CSR, Section 10; FpS-AS-201 CSR, Section 10; FpS-AS-202 CSR, Section 10; FSS-AS-305 CSR, Section 10; FSS-AS-201 CSR, Section 10; FpS-AS-101 CSR, Section 10; FpS-AS-102 CSR, Section 10; and FSS-AS-10042 CSR, Section 10.

[a] 2 inhalations twice a day.
[b] 1 inhalation per day.
[c] Due to crossover design of the study, more than 1 treatment was received; however, patients are counted only once for the total.
[d] 2 inhalations per dose per day.
[e] 4 inhalations per dose per day.

bid=twice daily; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol multidose dry powder inhaler; HFA=hydrofluoroalkane.

Adverse events

The adverse event profile was similar in the Phase 3 and Phase 2/3 Safety Pools and in the long-term Study FSS-AS-305 and generally consistent with the established adverse event profile of Advair Diskus and Advair HFA. Abnormalities identified upon oropharyngeal examination were reported as adverse events of oral candidiasis, and included oral fungal infection, oropharyngeal candidiasis, and oropharyngitis fungal.

Overview of Treatment-Emergent Adverse Events

The treatment-emergent adverse event profile was found to be similar within and across studies for all FS MDPI treatment groups. The few instances of differences need to be considered in the context of the longer duration of exposures in the FS MDPI groups relative to the placebo and the differences in design between the Phase 2 and Phase 3 studies.

Common Adverse Events

In the **Phase 3 Safety Pool** the incidence of patients who had treatment-emergent adverse events (TEAEs) was similar for FS MDPI treatment groups (36% to 42%) compared with the placebo group (36%). In the Phase 2/3 Safety Pool, the incidence of patients who had TEAEs was similar for FS MDPI treatment groups (36% to 42%) compared with the placebo group (33%).

In the Phase 3 Safety Pool, the System Organ Classes (SOCs) with the highest incidence of adverse events (across all treatment groups) were infections and infestations (17% to 29%); respiratory, thoracic and mediastinal disorders (5% to 11%); nervous system disorders (2% to 9%); musculoskeletal and connective tissue disorders (2% to 7%); gastrointestinal disorders (2% to 8%); and injury, poisoning and procedural complications (1% to 5%). All other SOCs had incidences of adverse events <5% in any FS MDPI treatment group. In the Phase 2/3 Safety Pool, the incidence of adverse events by SOCs had a similar distribution.

In both the Phase 3 and Phase 2/3 Safety Pools, 6 different treatment-emergent adverse events occurred in at least 3% of patients in any FS MDPI treatment group and were more common in any FS MDPI treatment group than in placebo-treated patients. These 6 PTs for which the incidence was higher in the FS MDPI-treated patients than in placebo were nasopharyngitis, cough, headache, URI, back pain, and oral candidiasis.

In **Study FSS-AS-305**, the incidence of patients who had severe treatment-emergent adverse events, serious treatment-emergent adverse events, or an adverse event causing withdrawal was low (≤10% in any treatment group). The incidence of patients who had treatment-related treatment-emergent adverse events was lower among the FS MDPI treatment groups (8% for both mid- and high-strength groups) compared with the Advair Diskus treatment groups (10% and 18% for mid- and high-strength groups, respectively). The incidence of patients who had treatment-emergent adverse events was similar in all study groups (65% to 77%). The SOCs with the highest incidence of adverse events across the treatment groups were infections and infestations (42% to 59%); respiratory, thoracic and mediastinal disorders (17% to 28%); injury, poisoning and procedural complications (2% to 17%); gastrointestinal disorders (6% to 15%); musculoskeletal and connective tissue disorders (2% to 15%); nervous system disorders (2% to 12%); general disorders and administration site conditions (5% to 11%).

In the Phase 2/3 and Phase 3 Safety Pools, asthma exacerbations occurred at a similar frequency within and across all FS MDPI treatment groups (1% to 4%). Asthma exacerbations were reported at a higher percentage of patients treated with placebo (11% to 12%). The incidence of severe asthma exacerbations was low (≤1%) across all treatment groups. The incidence and severity of adverse events were not dependent on disease severity.

The incidence and severity of adverse events were similar in Studies FSS-AS-301 and FSS-AS-30017, despite a milder asthma severity in Study FSS-AS-301. Similarly, the incidence and severity of adverse events did not vary systematically with the dose of ICS used (an indication of a patient's asthma severity).

Table 29: (Clinical Overview): Brief Summary of Treatment-Emergent Adverse Events by Treatment Group: Long-Term Safety Study FSS-AS-305

	ICS cohort				ICS/LABA cohort			
	Mid-strength		High-strength		Mid-strength		High-strength	
Number of patients with	Fp MDPI 100 mcg N=127	FLOVENT HFA 110 mcg N=42	Fp MDPI 200 mcg N=125	FLOVENT HFA 220 mcg N=41	FS MDPI 100/12.5 mcg N=120	ADVAIR DISKUS 250/50 mcg N=41	FS MDPI 200/12.5 mcg N=133	ADVAIR DISKUS 500/50 mcg N=44
At least 1 TEAE[a]	85 (67)	29 (69)	83 (66)	29 (71)	92 (77)	29 (71)	86 (65)	30 (68)
At least 1 severe TEAE[b]	8 (6)	3 (7)	11 (9)	3 (7)	8 (7)	1 (2)	12 (9)	3 (7)
At least 1 treatment-related TEAE	10 (8)	2 (5)	6 (5)	5 (12)	9 (8)	4 (10)	11 (8)	8 (18)
At least 1 severe treatment-related TEAE	0	0	0	0	0	0	0	0
At least 1 serious TEAE	7 (6)	2 (5)	8 (6)	3 (7)	6 (5)	2 (5)	13 (10)	3 (7)
At least 1 TEAE causing withdrawal	2 (2)	1 (2)	0	1 (2)	3 (3)	2 (5)	0	1 (2)
At least 1 nonserious TEAE	85 (67)	27 (64)	82 (66)	29 (71)	91 (76)	28 (68)	85 (64)	29 (66)
At least 1 TEAE resulting in death	0	0	0	0	0	0	0	0

Source: Module 2.7.4, Table 28; FSS-AS-305 CSR, Summary 15.3.1.1.1.
[a] Patients may have reported more than 1 adverse event.
[b] If patients report an adverse event more than once, the greatest severity is presented for that event.
Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; HFA=hydrofluoroalkane; ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; N=number of patients; TEAE=treatment-emergent adverse event.
Notes: The denominator for calculating percentages is the number of patients in the safety population in a given treatment group. Patients are counted only once in each category.
Table column titles reflect the treatment arm (product), as described in Module 2.7.3, Section 2.3.

Adverse Drug Reactions

The treatment-emergent adverse events that occurred in at least 3% of patients in any FS MDPI treatment group in the Phase 3 Safety Pool and were more common in FS MDPI-treated patients than placebo-treated patients, which are known common adverse reactions related to treatment with Fp/salmeterol in an asthma population, were nasopharyngitis, headache, cough, oral candidiasis (including oropharyngeal candidiasis, oral fungal infection, and oropharyngitis fungal), and back pain (Table below).

Treatment-emergent adverse events that occurred in at least 3% of patients in any FS MDPI treatment group in Study FSS-AS-305 are similar to the profile observed in the Phase 3 Safety Pool studies and are known common adverse reactions related to treatment with FS in an asthma population, including urinary tract infection (URI) or inflammation, bronchitis, cough, headache, nausea, vomiting, and musculoskeletal pain. Overall, a review of the reported adverse events revealed no new safety issues with FS MDPI treatment compared with Advair Diskus or Seretide Accuhaler.

Table 30: Adverse Reactions With ≥3% Incidence With FS MDPI, and More Common Than Placebo in Patients With Asthma: Phase 3 Safety Pool

	Number (%) of patients[a]								
		Fp MDPI (mcg bid)				FS MDPI (mcg bid)			
MedDRA 17.0 preferred term	Placebo N=273	50 N=129	100 N=274	200 N=146	Combined N=549	50/12.5 N=128	100/12.5 N=269	200/12.5 N=145	Combined N=542
Number of patients with at least 1 adverse event	99 (36.3)	44 (34.1)	93 (33.9)	60 (41.1)	197 (35.9)	46 (35.9)	96 (35.7)	61 (42.1)	203 (37.5)
Nasopharyngitis	12 (4.4)	7 (5.4)	16 (5.8)	7 (4.8)	30 (5.5)	11 (8.6)	13 (4.8)	10 (6.9)	34 (6.3)
Headache	12 (4.4)	2 (1.6)	20 (7.3)	7 (4.8)	29 (5.3)	7 (5.5)	13 (4.8)	4 (2.8)	24 (4.4)
Cough	7 (2.6)	2 (1.6)	5 (1.8)	5 (3.4)	12 (2.2)	3 (2.3)	10 (3.7)	1 (0.7)	14 (2.6)
Oral candidiasis[b]	2 (0.7)	4 (3.1)	8 (2.9)	7 (4.8)	19 (3.5)	2 (1.6)	6 (2.2)	5 (3.4)	13 (2.4)
Back pain	5 (1.8)	0	4 (1.5)	2 (1.4)	6 (1.1)	4 (3.1)	2 (0.7)	0	6 (1.1)

Source: Module 2.7.4, Table 21.
[a] Patients may have reported more than 1 adverse event.
[b] Incidence includes adverse events of oral candidiasis, oral fungal infection, oropharyngeal candidiasis, and oropharyngitis fungal.
bid=twice daily; Fp MDPI=fluticasone propionate multidose dry powder inhaler; FS MDPI=fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in Phase 3 Safety Pool.
Note: Preferred terms are sorted by descending order of incidence within the FS-combined dose group.

Within the Phase 3 and Phase 2/3 Safety Pools, the reports of hypersensitivity reactions were low, no patients treated with FS MDPI had an adverse event of anaphylactic shock or angioedema, and the incidence of infections and infestations was similar across study groups. Treatment-emergent adverse events that occurred in at least 3% of patients in any FS MDPI treatment group in the Phase 3 Safety Pool and are known common adverse reactions related to treatment with Fp and salmeterol in patients with asthma include URI or inflammation, cough, headache, and musculoskeletal pain.

Adverse reactions observed in the studies with FS MDPI are the same as those already known for the combination of the active substances.

Serious adverse event/deaths/other significant events

Serious Adverse Events

A total of 22 patients reported treatment-emergent serious adverse events in the Phase 3 and Phase 2/3 Safety Pools, with a similar incidence observed among treatment groups (0% to 2%). Asthma was reported as a serious adverse event by 4 patients who received placebo and 1 patient who received FS MDPI 200/12.5 mcg. All other treatment-emergent serious adverse events occurred in 1 patient each. Only 3 patients (2 patients treated with placebo and 1 patient treated with FS MDPI 200/12.5 mcg) reported a serious adverse event (asthma) considered by the investigators to be related to the study drug; 3 events were considered by the investigators to be severe.

In Study FSS-AS-305, the incidence of serious adverse events (5% to 10%) was higher than that observed in the Phase 3 or Phase 2/3 Safety Pools (0% to 2%), with similar incidences across FS MDPI and Advair Diskus treatment groups. Forty-four patients had 1 or more serious adverse events during this study. The incidence of serious adverse events was similar between the treatment groups within the ICS/LABA cohorts. As in the Phase 3 and Phase 2/3 Safety Pools, asthma exacerbation was the most frequently reported serious adverse event (24 patients overall): FS MDPI treatment groups (3% to 6%) and Advair Diskus groups (2% to 5%). No serious adverse event in any of the FS MDPI groups was considered by the investigator to be related to study drug.

Death

One death was reported in the FS MDPI clinical development programme. The patient (in Study FSS-AS-30017) received FS MDPI 100/12.5 mcg and had a fatal adverse event of jaundice that was considered by the investigator and the sponsor to be not related to the study drug. The reported cause of the jaundice was fulminant hepatitis progression. It was not known whether the patient had pre-existing abnormalities.

Adverse Events of Special Interest

A detailed evaluation of adverse events due to localised infections of the mouth and pharynx with Candida albicans, paradoxical bronchospasm and upper airway symptoms, immediate hypersensitivity reactions, evidence of immunosuppression, hypercorticism and adrenal suppression, reduction in bone mineral density or associated consequences (i.e., vertebral fractures), effects on growth, hypokalaemia and hyperglycaemia, potential cardiovascular and central nervous system (CNS) effects, glaucoma and cataracts, and eosinophilic conditions and Churg-Strauss Syndrome was performed to evaluate these known issues associated with the use of Advair Diskus.

Within the Phase 3 and Phase 2/3 Safety Pools, no new safety concerns were identified. Reports of hypersensitivity reactions were low, no patients treated with FS MDPI had an adverse event of hypersensitivity, anaphylactic shock, or angioedema, and the incidence of infections and infestations was similar across study groups. All of the reported hypersensitivity reactions were considered to be

not treatment related. In the long-term safety Study FSS-AS-305, 1 patient treated with FS MDPI 100/12.5 mcg reported an adverse event of mild angioedema that was considered by the investigator to be not related to study drug. There were no adverse event reports of hypercorticism, adrenal suppression, decreased bone mineral density or associated consequences (i.e., vertebral fractures), glaucoma, cataracts, eosinophilic conditions, or Churg-Strauss syndrome adverse events across the Phase 2 and Phase 3 studies.

Although 1 patient treated with placebo had mild bronchospasm in a Phase 3 study, there were no adverse event reports of bronchospasm in patients treated with FS MDPI across the Phase 2 and Phase 3 studies.

Adverse Events in Adolescents

FS MDPI was generally well tolerated in the adolescent population with an adverse event profile similar to that seen in adults. There was no apparent difference in the adverse event profile with regard to age, nor was there evidence of an effect of age on the adverse event profile of FS MDPI as compared with placebo.

There were no reports of hypercorticism, adrenal suppression, decreased bone mineral density or associated consequences (i.e., vertebral fractures), glaucoma, cataracts, eosinophilic conditions, or Churg-Strauss syndrome adverse events across the Phase 2 and Phase 3 studies. Although effects on growth were not specifically evaluated in the FS MDPI programme, no adverse growth effects were reported for the 58 patients 12 to 17 years of age.

There was no apparent difference in the adverse event profile of FS MDPI compared to that of the already marketed combination.

Laboratory findings

No clinically meaningful differences (versus active comparators or placebo) or patterns of abnormality associated with FS MDPI administration were observed in clinical laboratory evaluation parameter values across the clinical studies included in the clinical development programme. There were no cases of elevated alanine aminotransferase ≥3× upper limit of normal (ULN) with elevated total bilirubin ≥2× ULN.

Although incidental abnormalities in potassium or glucose elevations were reported, there were no clinically meaningful differences (versus Advair Diskus or placebo) or potentially clinically important trends with FS MDPI administration.

Vital Signs and Electrocardiograms

There were no clinically meaningful differences (versus Advair Diskus or placebo) or potentially clinically important trends in vital signs (pulse rate and blood pressure), ECG intervals, or overall ECG assessments associated with FS MDPI administration across the clinical studies included in the clinical development programme. No controlled study data with continuous 24-hour ECG monitoring were collected using FS MDPI.

Physical Examinations

Across all clinical studies included in the clinical development programme, the greatest number of shifts in physical examination findings from normal to abnormal were reported for chest and lungs in the placebo groups. Overall, shifts from normal to abnormal in physical examination findings across all treatment groups were few and sporadic.

Oropharyngeal Examination

Safety was monitored by oropharyngeal examinations. Patients who demonstrated oropharyngeal signs consistent with oral candidiasis were evaluated by obtaining and analysing a swab of the suspect area. Any unfavourable, clinically significant change relative to baseline was reported as an adverse event. The incidence of positive swab test results was higher among patients treated with FS MDPI compared with placebo and similar to ADVAIR DISKUS.

In **the Phase 3 Safety Pool**, the incidence of patients who reported an adverse event of oral candidiasis, including oropharyngeal candidiasis, appeared to be dose-related with higher incidences reported in FS MDPI-treated patients (1.6% to 3.4%) compared with placebo-treated patients (0.7%). As seen with other fluticasone-containing products, the incidence of oral candidiasis appears to be related to the dose of fluticasone.

In **the Phase 2/3 Safety Pool**, the incidence oral candidiasis, including oral fungal infection, oropharyngeal candidiasis, and oropharyngitis fungal, was higher in the FS MDPI-treated patients (1.6% to 3.4%) compared with the placebo group (0.4%).

In the long-term study (**Study FSS-AS-305**), the incidence of oral candidiasis was highest in patients treated with high-dose ADVAIR DISKUS (11%). The incidence of oral candidiasis was similar across the remaining treatment groups across the ICS/LABA cohorts (4% to 5%).

Asthma Exacerbations

Asthma exacerbations were categorised as mild, moderate, or severe at the investigator's discretion. Severe asthma exacerbations were defined as requiring systemic corticosteroids for ≥3 days, hospitalisation, or emergency room visitation and were also labelled as serious adverse events in the Phase 3 and FSS-AS-305 studies.

In the Phase 2/3 and Phase 3 Safety Pools, asthma exacerbations occurred at a lower frequency within and across all FS MDPI treatment groups (1% to 4%) compared to placebo (11% to 12%); the incidence was highest in the placebo group in Study FSS-AS-30017, reflecting the more severe disease in this study. The incidence of severe asthma exacerbations was low (≤1%) across all treatment groups.

The incidence of asthma exacerbations that were recorded as serious adverse events in Study FSS-AS-305 was primarily a result of the protocol definition. Initially, an asthma exacerbation was reported as a serious adverse event if it met the criteria for a severe asthma exacerbation. After a protocol amendment, however, an asthma exacerbation was reported as a serious adverse event only if it met the standard criteria for a serious adverse event.

Within the ICS/LABA cohort in Study FSS-AS-305, the incidence of asthma exacerbation regardless of severity was similar between patients treated with FS MDPI and those treated with Advair Diskus at the mid-strength (13 [11%] and 5 [12%] patients, respectively). However, in the high-strength ICS/LABA cohort, the incidence was greater in the FS MDPI group (20 [15%] patients) than in the Advair Diskus group (3 [7%] patients). This open-label safety study was not designed to evaluate treatment differences in asthma exacerbation incidence. Prior history of asthma exacerbations was not collected and was not used to ensure proper balance in randomisation across the treatment groups. Thus, ad hoc statistical analyses were performed to determine if the incidence of asthma exacerbations was different across treatment groups. This analysis indicated that the incidence of asthma exacerbation events was not different between the FS MDPI and Advair Diskus groups, at both the mid- and the high-strengths in the ICS/LABA cohorts. The Applicant considered that the most likely explanation for the apparent differences is the rarity of the events and the smaller numbers of patients in the active comparator groups relative to the study drug groups (3:1 randomisation ratio).

<u>Urinary Cortisol Assessments</u>

Exogenously administered ICSs can result in suppression of endogenous corticosteroid production, especially at higher doses, thus 24-hour urine cortisol assessments were performed in Studies FSS-AS-305 and FpS-AS-202. Differences in urine cortisol between treatment groups within cohorts were minimal, and there was no apparent trend for greater or lesser changes for study drug treatment compared with active comparator treatment. The magnitude of the changes did not appear to increase between weeks 14 and 26. In Study FSS-AS-305, there was no apparent trend for greater or lesser changes from baseline in urine cortisol level for FS MDPI or Advair Diskus groups. Adverse events associated with low urine cortisol findings were not reported for any patients in the FS MDPI or Advair Diskus groups.

Safety in special populations

There was no apparent evidence of an effect of sex (male or female), age (12 to 17 years, 18 to 64 years, or ≥65 years), or race (white, black, or other races) in subgroups with reasonable sample sizes (i.e. >10) on the adverse event profile of FS MDPI as compared with active comparators or placebo. Thus, the applicant concluded that no dose adjustment for these factors is needed.

The incidence of adverse events was higher among patients in the US compared with the non-US but appeared to be balanced between placebo and active treatment groups.

Adolescent population

FS MDPI was generally well tolerated in the adolescent population with an adverse event profile similar to that seen in adults. There was no apparent difference in the adverse event profile with regard to age, nor was there evidence of an effect of age on the adverse event profile of FS MDPI as compared with placebo.

Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women that specifically test the effects of FS MDPI on pregnancy. However, the comparator products, Advair Diskus or Seretide Accuhaler, are recommended for use during pregnancy only if the potential benefits justify the risk to the foetus. Current asthma guidelines call for the use of moderate dose ICSs or corticosteroids with a LABA, in the treatment of moderate asthma in pregnant women and for combination therapy in severe asthma.

Analyses of human birth defect databases have demonstrated a possible association between ICS usage and isolated anorectal atresia. A combination of a beta-agonist and ICS was associated with an increased risk of omphalocele and renal dysplasia. Since the data are insufficient to determine if there is any added risk to the foetus from the treatment, FS MDPI should be used during pregnancy only if the potential benefits outweigh the potential risks.

There are also no well-controlled human studies that have investigated the effects of FS MDPI on pre-term labour or labour at term. Because of the potential for beta-agonist interference with uterine contractility, use of FS MDPI during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

There are no data from controlled trials on the use of FS MDPI by nursing mothers. It is possible that very low concentrations of Fp and salmeterol may appear in breast milk, but they are unlikely to affect the nursing infant.

The following are known from the already approved combination:

Fertility

There are no data in humans. However, animal studies showed no effects of salmeterol or fluticasone propionate on fertility.

Pregnancy

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity related to Seretide. Animal studies have shown reproductive toxicity after administration of β2 adrenoreceptor agonists and glucocorticosteroids.

Administration of Seretide to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women.

Breastfeeding

It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.

Studies have shown that salmeterol and fluticasone propionate, and their metabolites, are excreted into the milk of lactating rats.

A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Seretide therapy considering the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions have not been studied in the FS MDPI clinical programme, however drug-drug interactions with the components contained in FS MDPI have been described for Advair Diskus and Seretide Accuhaler.

The drug-drug interactions of the already marketed product have been included in the approved SmPC in section 4.5 Interaction with other medicinal products and other forms of interaction.

No additional drug-drug interactions were observed during the trials with FS MDPI.

Hepatic and Renal Impairment

Formal PK studies using FS MDPI have not been conducted in patients with hepatic or renal impairment.

Discontinuation due to adverse events

Withdrawals due to Adverse Events

In the Phase 3 and Phase 2/3 Safety Pools, the incidence of adverse events leading to withdrawal was low and similar across treatment groups (0% to 3%). In the Phase 2/3 Safety Pool, asthma was reported as an adverse event leading to withdrawal by 5 (1.0%) patients who received placebo and 1 patient (0.2%) who received FS MDPI 200/12.5 mcg.

Similar rates of withdrawal due to worsening asthma were seen among patients who received the low and mid doses in Study FSS-AS-301 (FS MDPI 50/12.5mcg: <1%, FS MDPI 100/12.5 mcg: 0%) and in Study FSS-AS-30017 (FS MDPI 100/12.5 mcg: <1%). A slightly higher withdrawal rate of 3% due to worsening asthma was observed at the high dose of 200/12.5 mcg. Patients treated with FS MDPI in

each Phase 3 study withdrew due to worsening asthma at lower rates compared to patients who received placebo (Study FSS-AS-301: 3%; Study FSS-AS-30017: 13%).

Among the adverse events that led to withdrawal from the study, the adverse events of URI and tachycardia were considered related to treatment with FS MDPI.

In the long-term safety study, 11 patients overall withdrew from the study due to adverse events. No single adverse event preferred term was reported as a reason for withdrawal for more than 1 patient. Within and across the ICS/LABA cohorts, the incidence of these events was relatively similar. In the FS MDPI and Advair Diskus groups, the adverse events (in 1 patient for each group of events) of dizziness, nausea, and vomiting; gastroesophageal reflux disease; chest discomfort, feeling jittery, and cough; pain in extremity; rhinitis allergic; and asthma led to withdrawal from the study.

The percentage of withdrawals due to adverse events (~1%) is considered low. However, there were imbalances between FS MDPI and active comparator.

Post marketing experience

Cumulatively, from post-marketing data sources (including non-serious reactions originating from solicited reports), from the date of launch in April 2017 until August 2019, 108 case reports concerning Airduo Respiclick (salmeterol + Fp) were received and processed in the applicant global safety database. Out of these 108 cases, 19 were assessed as serious. Fifteen of these 19 cases were from the same literature article titled "Inhaled corticosteroid related adrenal suppression detected by poor growth and reversed with ciclesonide". None of these published cases are for FS MDPI/Airduo Respiclick as it was approved after the publication was submitted to the journal.

Although primary adrenal disorders are uncommon in this patient population and more likely to be associated with the use of systemic corticosteroids, adrenal suppression remains an important identified risk linked to fluticasone use. Systemic adverse effects may occur with any ICS, particularly at high doses prescribed for long periods.

From the efficacy point of view, no new significant efficacy or effectiveness information was revealed in the reporting period.

Overall, from the data reviewed and analysed originating from post-marketing sources, no new safety issues and no signals were identified during the reporting period.

There is no marketing experience with FS MDPI, since it has not been marketed yet. It appears that no new safety issues and no signals were identified during the reporting period for the combination of Fp and salmeterol.

2.6.1. Discussion on clinical safety

Introduction

A total of 9 clinical studies in adult and adolescent patients have been completed and support the safety of FS MDPI. The Phase 3 Safety Pool (Studies FSS-AS-301 and FSS-AS-30017) served as the primary dataset for presentation and discussion of the safety profile of FS MDPI. Additionally, results from the Phase 2/3 Safety Pool (Studies FSS-AS-301, FSS-AS-30017, FpS-AS-201, and FpS-AS-202), a 26-week, open-label, long-term safety study (Study FSS-AS-305), and the other Phase 1 and 2 studies (FSS-AS-201, FpS-AS-101, FpS-AS-102, and FSS-AS-10042) are presented where relevant as supportive information for safety assessment.

The demographics for the Phase 2/3 Safety Pool were overall similar to the reported prevalence of asthma in children, females, and males and are considered to be representative of the population proposed for treatment (i.e. patients who require regular treatment of asthma aged 12 years and older).

Patient exposure

A total of 3455 patients and healthy volunteers received at least 1 dose of study drug in the studies, of whom 904 received treatment with FS MDPI, all of whom received the doses proposed for commercialisation (FS MDPI 50/12.5, 100/12.5, and 200/12.5 mcg). A total of 2637 patients were randomly assigned to the 12-week studies FSS-AS-301, FSS-AS-30017, FpS-AS-201, and FpS-AS-202, and 2625 received at least 1 dose of randomised treatment. Of these, 2194 patients completed 12 weeks of treatment, of whom 519 patients received treatment with FS MDPI. In the 12-week studies, 542 patients received treatment with FS MDPI; all of whom received the doses proposed for commercialisation. A total of 674 patients were randomly assigned to the 26-week study (FSS-AS-305). Overall, 595 patients completed 26 weeks of treatment, of whom 226 patients received treatment with FS MDPI (FSS-AS-305).

Adverse events

The numbers of patients and healthy volunteers studied are considered sufficient for the well-studied and well-known fluticasone propionate and salmeterol active substances.

No new safety signals were detected during the phase 3 studies with FS MDPI.

A greater proportion of patients withdrew early because of worsening of asthma in the placebo compared to the active treatment groups. This was more evident in the Phase 2 studies where all patients meeting stopping criteria for worsening asthma were withdrawn, unlike in the Phase 3 studies. This resulted in a longer duration of exposure in the active treatment groups compared to the placebo group.

In the 3 Phase 2 studies and 3 Phase 3 studies, the safety results for FS MDPI were overall similar to those of the comparator marketed product Advair Diskus.

However, in Study FSS-AS-305, there were slight imbalances in the incidence of asthma exacerbations. Upon request by CHMP, the Applicant clarified that this safety study was not designed to detect differences in the incidences of asthma exacerbations, and there was no collection of baseline asthma exacerbation rates within the treatment groups. Moreover, asthma exacerbation events were relatively rare and, particularly in view of the 3:1 randomisation ratio, the imbalance seen was likely due to chance, according to the applicant. Furthermore, pre-amendment protocol, which stipulated that any severe asthma exacerbation had to be reported as a serious adverse event, may have inflated the number of asthma exacerbations that were considered serious adverse events. Numerically more asthma and severe asthma exacerbations were observed in the long-term study FSS-AS-305 than in both Studies FSS-AS-301 and FSS-AS-30017. While it is challenging to make direct comparisons between data from different studies, there are a number of factors that likely contributed to these observed differences. The patients enrolled in the FS MDPI treatment groups in Study FSS-AS-305 had relatively more severe asthma. Also, the fact that Study FSS-AS-305 was more than twice the duration of Study FSS-AS-30017 may have contributed to the larger number of asthma exacerbations observed. As a result, an ad hoc analysis was conducted to compare exacerbations between treatments. Considering that the analysis found no difference in asthma exacerbations between the treatments, the most likely explanation for the apparent differences is the rarity of the events and the smaller numbers of patients in the active comparator groups relative to the study drug groups (due to the 3:1 randomisation ratio in favour of the study drug groups). While the overall number of asthma

exacerbations reported in the study was low and analysis showed that there were no differences between treatment groups, asthma exacerbations were examined in subgroups by age, gender, and race. Within each treatment group, none of the subgroups was disproportionately affected with asthma exacerbations. Analyses of the combined data for FS MDPI and Advair Diskus determined that the percentages of patients with asthma exacerbations did not differ greatly across the subgroups. Subgroups with greater numbers of asthma exacerbations were part of subgroups that were much larger than the subgroups with smaller numbers of exacerbations, and this most likely accounted for the small differences. This was supported by CHMP.

The Applicant claimed that FS MDPI would offer an option for some patients who are unable to tolerate the currently available products, due to the lower doses presented within BroPair Spiromax. Nevertheless, it should be noted that no large difference in safety profiles were seen when comparing the FS MDPI to Advair Diskus. Furthermore, the applicant confirmed that the clinical development programme for FS MDPI did not include clinical trials designed to assess superiority of the safety profile of FS MDPI versus Advair Diskus, and no a priori statistical analysis was implemented to compare the safety profiles of the 2 ICS/LABA treatments. The Applicant has provided evidence that the MDPI device is most likely safe when used with the SABA rescue medication albuterol. In the case of FS MDPI, significantly lower amounts of both fluticasone and salmeterol are used which could probably be associated with lesser adverse events compared to approved products. However, based on the clinical safety design, no firm conclusion can be made.

Frequently reported adverse events that occurred in at least 3% of FS MDPI-treated patients and more commonly than in patients treated with placebo included nasopharyngitis, cough, URI, and headache, which were not more common among active treatment patients relative to placebo, and oral candidiasis, which occurred primarily among active treatment patients as expected with the drug class.

Serious adverse event/deaths

There was no apparent difference in the adverse event profile of FS MDPI compared to that of the already marketed combination.

One death was reported in the FS MDPI clinical development programme which was considered by the investigator and the sponsor not to be related to the study drug.

Laboratory findings

No clinically meaningful differences (versus active comparators or placebo) or patterns of abnormality associated with FS MDPI administration were observed in clinical laboratory evaluation parameter values across the clinical studies included in the clinical development programme. This was agreed by CHMP.

Safety in special populations

There was no apparent evidence of an effect of sex (male or female), age (12 to 17 years, 18 to 64 years, or ≥65 years), or race (white, black, or other races) in subgroups with reasonable sample sizes (i.e. >10) on the adverse event profile of FS MDPI as compared with active comparators or placebo. Thus, the applicant concluded that no dose adjustment is needed.

Safety in patients from Studies FSS-AS-301 and FSS-AS-30017 who were treated with FS MDPI aged 65 years and older was reviewed in detail upon request by CHMP. In these studies, there were no serious adverse events or deaths reported in the patients aged 65 years and older. In the other studies (Studies FpS-AS-201 and FSS-AS-305), there were a total of 6 patients, aged 65 years and older, who experienced serious adverse events [Study FpS-AS-201: 1 serious adverse event of volume depletion (placebo); Study FSS-AS-305: 1 serious adverse event of malignant melanoma (Advair Diskus 250/50 mcg), 1 serious adverse event of arthritis (FS MDPI 200/12.5 mcg), 1 serious adverse event of

pneumonia (Advair Diskus 500/50 mcg), 1 serious adverse event of basal cell carcinoma (FS MDPI 200/12.5 mcg), and 1 serious adverse event of pulmonary mass, benign nodule (Fp MDPI 200 mcg)]. Overall, for the FS MDPI treatments in Studies FSS-AS-301 and FSS-AS-30017, the incidence of total adverse events in patients aged 65 years and older was slightly higher than that in patients younger than 65 years old (42.6% vs 36.9%, respectively), a difference reflective of the increased prevalence of comorbid conditions in the elderly. The evaluation of safety concluded that the overall incidence of adverse events was comparable between the younger and older age groups. The events occurring with a slightly increased incidence in the elderly group are common in this age group. Thus, there were no trends to suggest that the older population differs substantially from the rest of the population with respect to safety.

Upon request by CHMP, the applicant clarified that the safety profile of BroPair Spiromax did not differ between adolescent patients and adults. Although the number of adolescents included was rather limited, CHMP agreed that the available safety data are considered sufficient for the evaluation of the safety profile of FS MDPI in adolescents.

FS MDPI demonstrated a favourable safety profile in the regular treatment of asthma in patients aged 12 years and older. The results from both pooled analyses and individual studies evaluating FS MDPI treatment are consistent with the extensively characterised profile of the currently available inhaled ICS/LABA combination drug, Seretide Accuhaler, and include URI, nasopharyngitis, sinusitis, oral candidiasis, cough, bronchitis, headache, nausea, vomiting, and musculoskeletal pain. No new safety issues were identified for all doses of FS MDPI evaluated.

Safety related to drug-drug interactions

Drug-drug interactions have not been studied in the FS MDPI clinical programme, however drug-drug interactions with the components contained in FS MDPI have been described for Advair Diskus and Seretide Accuhaler. Those have been adequately reflected in the SmPC.

Discontinuations due to adverse events

The percentage of withdrawals due to adverse events (~1%) is considered low.

Long-Term Safety

The known history of systemic and local corticosteroids and β2-adrenoceptor agonist drugs has shown that long-term use may result in immunosuppression, hypercorticism and adrenal suppression, reduction in bone mineral density or associated consequences (i.e. vertebral fractures), growth effects, cardiovascular effects, CNS effects, and glaucoma and cataracts, especially at higher doses. ICS use in patients with asthma has not been associated with evidence of immunosuppression, nor was any evidence of immunosuppression found in the Phase 3 or Phase 2/3 Safety Pools. In the long-term study (Study FSS-AS-305), there was no evidence of opportunistic or severe infections suggestive of immunosuppression with FS MDPI or Advair Diskus treatment. No instances of the adverse events hypercorticism and adrenal suppression, reduction in bone mineral density or associated consequences (i.e. vertebral fractures), growth effects, and glaucoma and cataracts were observed. Nevertheless, and in line with similar products of the same class, appropriate warning has been included in section 4.4. of the SmPC.

Overall, there were no safety concerns for any of the 3 dose strengths of FS MDPI. The clinical safety development programme has confirmed that FS MDPI is a well-tolerated and effective treatment for adult and adolescent patients with asthma. The number of studies as well as the number of adult patients (<65 years of age) are considered sufficient to draw conclusions on the safety of the combination of fluticasone propionate and salmeterol, especially when combination of the same active

substances have been extensively studied, approved and marketed (e.g. Advair Diskus or Seretide Accuhaler).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the clinical safety assessment of FS MDPI is considered comprehensive and adequate to support an approval of the mid- and high-dose strengths for the treatment of Asthma in both Adult and adolescents aged 12 years and older.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Paradoxical bronchospasm • Systemic effects of corticosteroids (including growth retardation in adolescents 12 years and older) • Life-threatening and fatal asthma events with long-acting adrenergic β2-receptor agonists
Important potential risks	• Risk of prescribing error (confusion between the dosages) with potential inadequate control of asthma • Drug interactions (with β-adrenergic blockers and strong inhibitors of CYP3A4)
Missing information	• Use in pregnant or breastfeeding women

Pharmacovigilance plan

Additional pharmacovigilance requirements 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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT IDENTIFIED RISKS		
Paradoxical bronchospasm	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. Recommendation to discontinue use immediately in case of paradoxical bronchospasm in SmPC section 4.4. Wording regarding bronchospasms response to a rapid-acting bronchodilator included in SmPC section 4.4. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Systemic effects of corticosteroids (including growth retardation in adolescents 12 years of age and older)	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL sections 2 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Life-threatening and fatal asthma events with long-acting adrenergic β2 receptor agonists	**Routine risk minimisation measures:** SmPC section 4.4. Warning that sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. PL sections 3 and 4. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT POTENTIAL RISKS		
Risk of prescribing error (confusion between the dosages) with potential inadequate control of asthma	**Routine risk minimisation measures:** SmPC section 4.2. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Drug interactions (with β-adrenergic blockers and strong inhibitors of CYP3A4)	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.5. PL section 2. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
MISSING INFORMATION		
Use in pregnant or breastfeeding women	**Routine risk minimisation measures:** SmPC section 4.6. PL section 2. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 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 Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 27.01.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant indicated the active substances salmeterol/fluticasone propionate contained in the above medicinal product to be considered as a known active substance.

2.10. Product information

2.10.1. 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

3.1. Therapeutic Context

3.1.1. Disease or condition

Asthma is a chronic inflammatory disorder of the airways associated with airways inflammation and hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction. Patients with asthma can experience exacerbations that may be life threatening and carry a significant burden to patients and the community.

Asthma is a common disease affecting an estimated 340 million people worldwide and despite existing therapies, there are still significant unmet medical needs. The Global Burden of Asthma Report estimates that 23.7 million disability-adjusted life years are lost annually due to asthma, representing 1% of the total global burden. According to the World Health Organization (WHO) estimates, there were 383,000 deaths due to asthma in 2015.

3.1.2. Available therapies and unmet medical need

The long-term treatment goals are symptom control and risk reduction. Symptom control aims to have only occasional daytime symptoms without sleep disturbance or exercise limitation. Risk reduction involves preventing exacerbations, preserving lung function and avoiding asthma deaths.

Patients not adequately controlled with a maintenance low dose ICS and 'as needed' short-acting beta2-agonists or LABA (GINA step 2 and 3) have the following treatment options in addition to optimising treatment compliance and modifying risk factors;

- Combination low dose LABA/ICS with as needed short acting beta2-agonists
- Combination low dose formoterol/ICS maintenance and reliever.

The Applicant developed the FS MDPI, a multidose dry powder inhaler with the combination of Fp, an ICS, and salmeterol, a LABA. The FS MDPI has been developed to supply multiple dosage strengths of Fp with a fixed dosage of salmeterol (50/12.5 [low], 100/12.5 [mid], and 200/12.5 [high] mcg) to allow treatment of the entire spectrum of asthma patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonists.

3.1.3. Main clinical studies

To demonstrate the efficacy of FS MDPI, 2 replicate, placebo-controlled, randomised, parallel-group, 12-week Phase 3 efficacy and safety studies (FSS-AS-301 and FSS-AS-30017) in adult and adolescent patients (12 years of age or older with baseline FEV_1 40% to 85% of predicted normal) with asthma to evaluate the efficacy of FS MDPI across a spectrum of asthma severities were conducted. In addition to these studies, a 26-week, open-label, long-term safety and efficacy study with the mid- and high-strength doses of FS MDPI was conducted (Study FSS-AS-305).

Studies FSS-AS-301 and FSS-AS-30017 were designed to show superiority of Fp (nominal doses of 50, 100, and 200 mcg) over placebo and to show superiority of the FS combination (nominal doses of 50/12.5, 100/12.5, and 200/12.5 mcg) over Fp in adults and adolescents in a broad range of asthma severity. The co-primary endpoints in both studies were the change from baseline in trough (morning

pre-dose and pre-rescue bronchodilator) FEV1 at week 12 and the standardised baseline-adjusted post-dose FEV1 AUEC0-12h at the week 12 visit, analysed for the subset of approximately 300 patients who performed post-dose serial spirometry.

Demographics and baseline disease characteristics of patients enrolled to both pivotal studies were very similar.

In the 2 pivotal Phase 3 studies (FSS-AS-301 and FS-AS-30017), 1375 patients were randomised to Fp MDPI, FS MDPI, or placebo treatment, and of those patients, 1360 were included in the FAS population. The majority of patients in all treatment groups in the FAS population completed the study; only 9% of patients overall withdrew from the studies prematurely.

The long-term Study FSS-AS-305 was a 26-Week Open-Label Study to Assess the Long-Term Safety of Fluticasone Propionate Multidose Dry Powder Inhaler and Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler in Patients 12 Years of Age and Older with Persistent Asthma. The primary objective of the Study FSS-AS-305 was to evaluate the long-term safety of Fp inhalation powder in 2 strengths and FS inhalation powder in 2 strengths when administered with the Teva MDPI device over 26 weeks in patients 12 years of age and older with persistent asthma. The secondary objective of the study was to evaluate the safety of Fp MDPI in comparison to Flovent HFA and FS MDPI in comparison to Advair Diskus. The efficacy objective of the study was to evaluate the efficacy of Fp MDPI in comparison to Flovent HFA and FS MDPI in comparison to Advair Diskus. Therefore, efficacy was not a primary or secondary objective in this study. The principal efficacy variable was the change from baseline in trough FEV1 over the 26-week treatment period.

Demographic characteristics in Study FSS-AS-305 were generally well-balanced across the treatment groups and similar to the pooled and individual Phase 3 studies.

In the long-term safety Study FSS-AS-305, 674 patients were randomised to receive Fp MDPI, FS MDPI, FLOVENT HFA, or Advair Diskus, and 673 patients received at least 1 dose of study drug and were evaluated for safety in the study. A total of 79 (12%) patients withdrew from the study.

A monotherapy of Fp, fluticasone propionate multidose dry powder inhaler (Fp MDPI), was included in many of the studies and is mentioned in this submission, but the Fp MDPI monotherapy product is not part of this submission and was not submitted for approval in the EU.

This clinical development programme attempted to confirm that FS MDPI is an effective and well-tolerated treatment for adult and adolescent patients with asthma.

3.2. Favourable effects

In both pivotal studies (FSS-AS-301 and FSS-AS-30017), the primary objectives were met.

- Low-strength Combination (FS MDPI 50/12.5 mcg)

The low-strength combination was assessed in Study FSS-AS-301.

Change from baseline in trough FEV_1

The change from baseline in trough FEV_1 was 0.319 L for the FS MDPI low-strength combination compared with 0.053 L for placebo and 0.172 L for Fp MDPI 50 mcg. When FS MDPI 50/12.5 mcg was compared to placebo, the difference was 0.266 L ($p<0.0001$), and when compared to Fp MDPI 50 mcg, the difference was 0.147 L ($p=0.0022$).

Standardised baseline-adjusted FEV_1 $AUEC_{0-12h}$

The change from baseline post-dose FEV1 AUC0-12h was 0.399 L for the FS MDPI low-strength combination (50/12.5 mcg) compared to 0.074 L for placebo and 0.268 L for Fp MDPI 50 mcg. When FS MDPI 50/12.5 mcg was compared to placebo, the difference was 0.325 L (p=0.0000) and when compared to Fp MDPI 50 mcg, the difference was 0.131 L (p=0.0322).

- *Mid-strength Combination (FS MDPI 100/12.5 mcg)*

Change from baseline in trough FEV_1

The mid-strength combination was assessed in patients with both mild to moderate asthma (Study FSS-AS-301) and moderate to severe asthma (Study FSS-AS-30017).

In patients with mild to moderate asthma, the change from baseline in trough FEV_1 was 0.315 L for the FS MDPI mid-strength combination compared to 0.053 L for placebo and 0.204 L for Fp MDPI 100 mcg. When FS MDPI 100/12.5 mcg was compared to placebo, the difference was 0.262 L (p<0.0001), and when compared to Fp MDPI 100 mcg, the difference was 0.111 L (p=0.0202).

In patients with moderate to severe asthma, the change from baseline in trough FEV_1 was 0.271 L for the FS MDPI mid-strength combination compared to -0.004 L for placebo and 0.119 L for Fp MDPI 100 mcg. When FS MDPI 100/12.5 mcg was compared to placebo, the difference was 0.274 L (p<0.0001), and when compared to Fp MDPI 100 mcg, the difference was 0.152 L (p=0.0005).

Standardised baseline-adjusted FEV1 AUEC0-12h

In patients with mild to moderate asthma, the change from baseline post-dose FEV1 AUC0-12h was 0.408 L for the FS MDPI mid-strength combination compared to 0.074 L for placebo and 0.254 L for Fp MDPI 100 mcg When FS MDPI 100/12.5 mcg was compared to placebo, the difference was 0.335 L (p=0.0000), and when compared to Fp MDPI 100 mcg, the difference was 0.154 L (p=0.0076).

In patients with moderate to severe asthma, the change from baseline post-dose FEV1 AUC0-12h was 0.442 L for the FS MDPI mid-strength combination compared to 0.121 L for placebo and 0.260 L for Fp MDPI 100 mcg. When FS MDPI 100/12.5 mcg was compared to placebo, the difference was 0.322 L (p=0.0000), and when compared to Fp MDPI 100 mcg, the difference was 0.182 L (p=0.0010).

- *High-strength Combination (FS MDPI 200/12.5 mcg)*

Change from baseline in trough FEV_1

The change from baseline in trough FEV_1 was 0.272 L for the FS MDPI high-strength combination compared to -0.004 L for placebo and 0.179 L for Fp MDPI 200 mcg. When FS MDPI 200/12.5 mcg was compared to placebo, the difference was 0.276 L (p-value<0.0001), and when compared to Fp MDPI 200 mcg, the difference was 0.093 L (p=0.0309). The difference between FS MDPI and Fp MDPI for the trough FEV_1 endpoint reflects the contribution of salmeterol at the end of the dosing period.

Standardised baseline-adjusted FEV1 AUEC0-12h

The change from baseline post-dose FEV1 AUC0-12h was 0.446 L for the FS MDPI high-strength combination compared to 0.121 L for placebo and 0.267 L for Fp MDPI 200 mcg. When FS MDPI 200/12.5 mcg was compared to placebo, the difference was 0.326 L (p=0.0000), and when compared to Fp MDPI 200 mcg, the difference was 0.179 L (p=0.0009). The difference between the high-strength FS MDPI and Fp MDPI provides evidence for the significant added benefit of salmeterol in the high-strength combination.

Comparisons of combination therapy with monotherapy were not controlled for multiplicity but indicated an overall improvement for FS MDPI 50/12.5 mcg compared with Fp MDPI 50 mcg and Fp MDPI 100 mcg and for FS MDPI 100/12.5 mcg compared with Fp MDPI 100 mcg in Study FSS-AS-301

and improvement for FS MDPI 100/12.5 mcg compared with Fp MDPI 100 mcg and Fp MDPI 200 mcg and for FS MDPI 200/12.5 mcg compared with Fp MDPI 200 mcg in Study FSS-AS-30017.

Pooled data from Studies FSS-AS-301 and FSS-AS-30017 by dose group showed similar baseline trough FEV_1 values across all FS MDPI and placebo groups. At week 12, all FS MDPI dose groups showed greater increases in mean change trough FEV_1 (0.340, 0.300, and 0.290 L in the 50/12.5, 100/12.5, and 200/12.5 mcg groups, respectively) than the placebo group (0.104 L). At week 12, the increase in mean baseline-adjusted FEV_1 $AUEC_{0-12h}$ was similar (0.366, 0.356, and 0.369 L) in the FS MDPI 50/12.5, 100/12.5, and 200/12.5 mcg groups, respectively. All FS MDPI dose groups showed greater increases in mean baseline-adjusted FEV_1 $AUEC_{0-12h}$ than the corresponding Fp MDPI groups (0.212, 0.192, and 0.194 L in the 50, 100, and 200 mcg groups, respectively) and the placebo group (0.032 L).

Secondary efficacy endpoints:

Low strength: FS MDPI 50/12.5 mcg compared to Fp MDPI 50 mcg

The change from baseline in the weekly average daily rescue medication use over 12 weeks decreased by a greater extent with FS MDPI 50/12.5 mcg compared to Fp MDPI 50 mcg (difference of least squares [LS] mean: -0.239 puffs/day; nominal p=0.0640).

Medium strength: FS MDPI 100/12.5 mcg compared to Fp MDPI 100 mcg

The mid-strength combination demonstrated a significant improvement over the mid-strength mono-product for the AQLQ, as well as for daily rescue medication use and the percentage of asthma control days.

High strength: FS MDPI 200/12.5 mcg compared to Fp MDPI 200 mcg

The high-strength combination demonstrated a significant improvement over the high-strength mono-product for the 3-following symptom-related endpoints: the change from baseline in the weekly average of the daily asthma symptom score; the weekly average of daily rescue medication use and the percentage of symptom-free days.

Note: the symptomatic asthma endpoints were included in secondary pre-specified analyses, and thus were not adequately powered to show a statistically significant effect.

3.3. Uncertainties and limitations about favourable effects

The duration of both pivotal studies was only 12 weeks; however, it is considered acceptable for substances with a well-known efficacy profile. In both pivotal studies, the comparison of FS MDPI vs Fp MDPI for trough FEV1 was not included in the primary endpoint. However, a sequential approach was used in the study design, first comparing the mono-product to placebo to demonstrate a significant effect, and then comparing the combination to the mono-product, to prove the efficacy of Fp and the combination. Moreover, two different endpoints were used to demonstrate efficacy of the ICS and the LABA included in FS MDPI, which act by different mechanisms to improve pulmonary function.

An additional benefit was seen when salmeterol was added to FS MDPI (fixed-dose combination containing fluticasone propionate and salmeterol), however better clinical efficacy results were reported for the mid- and high-strengths investigated in the pivotal studies and therefore only the mid- and high strengths are considered to be approvable. The effect observed with the mid- and high dose is considered clinically significant and relevant for the intended population.

For BroPair Spiromax, the following indication was initially proposed by the applicant:

BroPair Spiromax is indicated for use in adults and adolescents 12 years and older.

BroPair Spiromax is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting β_2 agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 agonist.

Nevertheless, the second part of the indication: 'patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 agonist' (substitution indication) was not adequately supported by the clinical development programme. Therefore, interchangeability between FS MDPI and the approved comparator Advair Diskus (or other approved products) cannot be claimed. The applicant agreed to amend the indicated to the 'step-up' part only (i.e. 'patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2 agonist') in line with the clinical efficacy data provided in support of this application.

The final indication agreed by CHMP is as follows:

BroPair Spiromax is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonists.

Moreover, as the doses to be used with BroPair Spiromax do not correspond to any approved doses for other salmeterol/fluticasone propionate containing products; the following text was added to section 4.2 of the SmPC to avoid any potential confusion and/or dosing errors:

'Note that the delivered doses for BroPair Spiromax are different from other salmeterol/fluticasone propionate containing products on the market. The products are thus not interchangeable on dose bases and different dose levels (including medium/high doses of fluticasone propionate) for different products do not necessarily correspond to each other.'

The data submitted for patients older than 65 years of age were considered to be limited by CHMP. Furthermore, there was a greater variability in the treatment responses observed in the >65 years of age subgroup. However, this could be attributed to the variation in a single response associated with a small sample size and not a unique characteristic of this population. Overall, it was considered that the older population did not respond differently to FS MDPI than the population as a whole. Thus, there is no need to adjust the dose in elderly patients.

3.4. Unfavourable effects

The safety profile of the individual active substances fluticasone propionate and salmeterol is generally well characterised either as monotherapy and/or double fixed dose combinations. The overall safety profile of BroPair Spiromax was consistent with the expected safety profile for these classes of drugs used in the treatment of patients with asthma.

Overall, 3455 patients and healthy volunteers received at least 1 dose of study drug in the studies, of whom 904 received treatment with FS MDPI, all of whom received the doses proposed for commercialisation (FS MDPI 55/14, 113/14, and 232/14 mcg; metered doses).

Adverse reactions that occurred in at least 3% of patients in any FS MDPI treatment group included urinary tract infection (URI) or inflammation, cough, headache, and musculoskeletal pain, which were more common among active treatment patients relative to placebo, and oral candidiasis, which occurred primarily among active treatment patients, as expected with this class of products. Those are known common adverse reactions related to treatment with fluticasone propionate and salmeterol in patients with asthma. Few adverse events were reported for vital signs (specifically blood pressure), ECG, or cardiac abnormalities; however, there were no serious adverse events in these categories.

The reports of hypersensitivity reactions were low, no patients treated with FS MDPI had an adverse event of anaphylactic shock or angioedema, and the incidence of infections and infestations was similar across study groups.

A detailed evaluation of adverse events due to localised infections of the mouth and pharynx with C. albicans, paradoxical bronchospasm and upper airway symptoms, immediate hypersensitivity reactions, evidence of immunosuppression, hypercorticism and adrenal suppression, reduction in bone mineral density or associated consequences (i.e., vertebral fractures), effects on growth, hypokalaemia and hyperglycaemia, potential cardiovascular and CNS effects, glaucoma and cataracts, and eosinophilic conditions and Churg-Strauss Syndrome was performed to evaluate these known issues associated with the use of Advair Diskus or Seretide Accuhaler in an asthma population. No new safety concerns were identified. However, and in line with similar products of the same class, appropriate warning has been included in section 4.4. of the SmPC.

There were slight imbalances in the incidence of asthma exacerbations in the long-term safety Study FSS-AS-305. Numerically more asthma and severe asthma exacerbations were observed in the long-term study FSS-AS-305 than in both Studies FSS-AS-301 and FSS-AS-30017. However, an ad hoc analysis was conducted to compare exacerbations between treatments. Considering that the analysis found no difference in asthma exacerbations between the treatments, the most likely explanation for the apparent differences is the rarity of the events and the smaller numbers of patients in the active comparator groups relative to the study drug groups (due to the 3:1 randomisation ratio in favour of the study drug groups). Asthma exacerbations were examined in subgroups by age, gender, and race. Within each treatment group, none of the subgroups was disproportionately affected with asthma exacerbations. Analyses of the combined data for FS MDPI and Advair Diskus determined that the percentages of patients with asthma exacerbations did not differ greatly across the subgroups.

3.5. Uncertainties and limitations about unfavourable effects

The duration of the long-term safety study (FSS-AS-305) was considered to be short (i.e. six months safety study) and therefore uncertainties remain on the unfavourable effects that could arise with the use of FS MDPI in a real-world setting especially in the under-represented populations (i.e. adolescents and elderly patients). However, considering the well-recognised safety profile of fluticasone propionate and salmeterol, this study was considered adequate to assess the safety of BroPair Spiromax.

A greater proportion of patients withdrew early because of worsening asthma in the placebo group vs the active treatment groups. This was more evident in the Phase 2 studies where all patients meeting stopping criteria for worsening asthma were withdrawn, as opposed to the Phase 3 studies. This resulted in a longer duration of exposure in the active treatment groups vs the placebo group.

In the long-term safety Study FSS-AS-305, there were slight imbalances in the incidence of asthma exacerbations. This open-label safety study was not designed to detect differences in the incidences of asthma exacerbations (which were relatively rare) and there was no collection of baseline asthma exacerbation rates within the treatment groups, which can contribute to observed differences. The ad hoc statistical analyses of all asthma exacerbations and severe asthma exacerbations showed no

differences within cohorts between the respective study drug group and active comparator for each dose strength and with dose strengths combined, indicating that apparent differences are most likely due to chance.

While there was no apparent difference in the adverse event profile of FS MDPI compared to the safety profile of already marketed combination products containing the same actives substances, the significantly lower amounts of both fluticasone and salmeterol used in FS MDPI could be associated with lesser adverse events compared to approved products. However, since the clinical development programme for FS MDPI did not include clinical trials designed to assess superiority of the safety profile of FS MDPI versus Advair Diskus, and no a priori statistical analysis was implemented to compare the safety profiles of the 2 ICS/LABA treatments, no conclusion can be made.

3.6. Effects Table

Table 31: Effects Table for BroPair Spiromax in the indication for regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonists.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Trough FEV1	Change from baseline in trough FEV1 at week 12	(L)	*Fp 50*: 0.172 *Fp100:* 0.204 *FS 50/12.5:* 0.319 *FS 100/12.5:* 0.315	*Placebo:* 0.053	All groups statistically significantly different from placebo (p-values: Fp50: 0.0132, Fp100: 0.0017, FS50/12.5: 0.0000, FS100/12.5: 0.0000). No difference between FS groups. Both Fs groups significantly statistically different from Fp 100	Study FSS-AS-301
FEV1 AUEC0-12h	Standardised baseline-adjusted FEV1 AUEC 0-12h at week 12	(L)	*Fp 50:* 0.268 *Fp100:* 0.254 *FS 50/12.5:* 0.399 *FS 100/12.5:* 0.408	*Placebo: 0.074*	All groups statistically significantly different from placebo placebo (p-values: Fp50: 0.0012, Fp100: 0.0020, FS50/12.5: 0.0000, FS100/12.5: 0.0000). Both Fs groups statistically significantly different from Fp 100	Study FSS-AS-301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Trough FEV1	Change from baseline in trough FEV1 at week 12	(L)	*Fp 100:* 0.119 *Fp200:* 0.179 *FS 100/12.5:* 0.271 *FS 200/12.5:* 0.272	*Placebo:* -0.004	All groups statistically significantly different from placebo (p-values: Fp50: 0.0047, Fp100: 0.0000, FS50/12.5: 0.0000, FS100/12.5: 0.0000). No difference between FS groups. Both Fs groups statistically significantly different from Fp 200	Study FSS-AS-30017
FEV1 AUEC0-12h	Standardised baseline-adjusted FEV1 AUEC 0-12h at week 12	(L)	*Fp 100:* 0.260 *Fp200:* 0.267 *FS 100/12.5:* 0.442 *FS 200/12.5:* 0.446	*Placebo:* 0.121	All groups statistically significantly different from placebo (p-values: Fp50: 0.0108, Fp100: 0.0084, FS50/12.5: 0.0000, FS100/12.5: 0.0000). No difference between FS groups. Both Fs groups statistically significantly different from Fp 100	Study FSS-AS-30017
Unfavourable Effects						
URI	Upper respiratory tract infections	Percentage in the No. of events	*Fp 50:* 5% *Fp100:* 3% *FS 50/12.5:* 5% *FS 100/12.5:* 2%	Placebo 5%		Study FSS-AS-301
Cough		Percentage in the No. of events	*Fp 50:* 2% *Fp100:* 3% *FS 50/12.5:* 2% *FS 100/12.5:* 4%	Placebo – 2%		Study FSS-AS-301
Headache		Percentage in the No. of events	*Fp 50:* 2% *Fp100:* 7% *FS 50/12.5:* 5% *FS 100/12.5:* 6%	Placebo – 4%		Study FSS-AS-301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Oral candidiasis		Percentage in the No. of events	*Fp 50:* 3% *Fp100:* 2% *FS 50/12.5:* 2% *FS 100/12.5:* 3%	Placebo – 1%		Study FSS-AS-301
Asthma exacerbations (moderate)		Percentage in the No. of events	*Fp 50:* 1% *Fp100:* 1% *FS 50/12.5:* 1% *FS 100/12.5:* 1%	Placebo – 5%		Study FSS-AS-301
URI		Percentage in the No. of events	*Fp 100:* 6% *Fp200:* 5% *FS 100/12.5:* 4% *FS 200/12.5:* 4%	Placebo – 5%		Study FSS-AS-30017
Upper respiratory tract infections		Percentage in the No. of events	*Fp 100:* 6% *Fp200:* 5% *FS 100/12.5:* 4% *FS 200/12.5:* 4%	Placebo – 2%		Study FSS-AS-30017
Cough		Percentage in the No. of events	*Fp 100:* 1% *Fp200:* 3% *FS 100/12.5:* 3% *FS 200/12.5:* 1%	Placebo – 3%		Study FSS-AS-30017
Headache		Percentage in the No. of events	*Fp 100:* 8% *Fp200:* 5% *FS 100/12.5:* 4% *FS 200/12.5:* 3%	Placebo: 5%		Study FSS-AS-30017
Oral candidaisis		Percentage in the No. of events	*Fp 100:* 3% *Fp200:* 5% *FS 100/12.5:* 1% *FS 200/12.5:* 2%	Placebo: 1%		Study FSS-AS-30017
Asthma exacerbations (moderate)		Percentage in the No. of events	*Fp 100:* 3% *Fp200:* 3% *FS 100/12.5:* 1% *FS 200/12.5:* 2%	Placebo: 13%		Study FSS-AS-30017
Upper respiratory tract infections		Percentage in the No. of events	FS 100/12.5: 18% FS 200/12.5: 18%	Advair Diskus250/50: 22% 500/50: 14%		Study FSS-AS-305
Cough		Percentage in the No. of events	FS 100/12.5: 12% FS 200/12.5: 6%	Advair Diskus 250/50: 5% 500/50: 2%		Study FSS-AS-305
Headache		Percentage in the No. of events	FS 100/12.5: 8% FS 200/12.5: 2%	Advair Diskus 250/50: 10% 500/50: 5%		Study FSS-AS-305
Oral candidiasis		Percentage in the No. of events	FS 100/12.5:4% FS 200/12.5: 4%	Advair Diskus 250/50: 5% 500/50: 11%		Study FSS-AS-305

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Asthma exacerbations (moderate)		Percentage in the No. of events	FS 100/12.5: 7% FS 200/12.5: 5%	Advair Diskus 250/50: 7% 500/50: 2%		Study FSS-AS-305

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Fixed-dose combination products containing a LABA and an ICS are considered as a standard therapy for patients with asthma. There are many LABA/ICS products with an established efficacy and safety profile available on the EU market including approved ICS/LABA containing the same actives substances as BroPair Spiromax and for which the clinical efficacy and clinical safety have been well characterised and demonstrated. The aim of the clinical programme for BroPair Spiromax was to identify doses of fluticasone propionate and salmeterol that were comparable in efficacy but with lower systemic exposure than the currently marketed products containing the same active substances (e.g. Advair Diskus, Seretide Accuhaler) and to confirm that BroPair Spiromax is an effective and well-tolerated treatment for adult and adolescent patients with asthma.

A broader indication in Asthma was initially sought. To support the initially proposed 'step-up' indication in Asthma *(i.e. patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2 agonist)*; two replicate, placebo-controlled, randomised, parallel-group, 12-week Phase 3 efficacy and safety studies (FSS-AS-301 and FSS-AS-30017) in adult and adolescent patients (12 years of age or older with baseline FEV_1 40% to 85% of predicted normal) with asthma to evaluate the efficacy of BroPair Spiromax low-, mid- and high- strengths (FS MDPI 50/12.5 mcg, FS MDPI 100/12.5 mcg and FS MDPI 200/12.5 mcg, respectively) across a spectrum of asthma severities were conducted.

In both pivotal studies (FSS-AS-301 and FSS-AS-30017), the primary objectives were met. When BroPair Spiromax low strength (FS MDPI 50/12.5 mcg) was compared to placebo, the difference was 0.325 L (p=0.0000). When BroPair Spiromax mid-strength (FS MDPI 100/12.5 mcg) was compared to placebo, the difference was 0.274 L (p<0.0001). When BroPair Spiromax high-strength (FS MDPI 200/12.5 mcg) was compared to placebo, the difference was 0.326 L (p=0.0000).
Comparisons of combination therapy (BroPair Spiromax FS MDPI) with monotherapy (Fp MDPI) were not controlled for multiplicity but indicated improvement for BroPair Spiromax compared with the ICS monotherapy (Fp MDPI) in both pivotal phase 3 studies.

Pooled data from both pivotal phase 3 Studies FSS-AS-301 and FSS-AS-30017 by dose group showed similar baseline trough FEV_1 values across all BroPair Spiromax (FS MDPI) and placebo groups. At week 12, all FS MDPI dose groups showed greater increases in mean change trough FEV_1 (0.340, 0.300, and 0.290 L in the 50/12.5, 100/12.5, and 200/12.5 mcg groups, respectively) than the placebo group (0.104 L). At week 12, the increase in mean baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ was similar (0.366, 0.356, and 0.369 L) in the FS MDPI 50/12.5, 100/12.5, and 200/12.5 mcg groups, respectively. All FS MDPI dose groups showed greater increases in mean baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ than the corresponding Fp MDPI groups (0.212, 0.192, and 0.194 L in the 50, 100, and 200 mcg groups, respectively) and the placebo group (0.032 L).

To support the initially proposed 'substitution' indication in Asthma *(i.e. patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist),* a 26-week, open-label, long-term

safety and efficacy study with the mid- and high-strength doses of BroPair Spiromax was conducted (Study FSS-AS-305). However, the study was not powered to show differences in efficacy. Thus, the substitution indication was not adequately supported by the clinical development programme and was therefore withdrawn by the applicant. In addition, interchangeability between BroPair Spiromax and the approved comparator Advair Diskus (or other approved products) cannot be claimed. This has been adequately reflected in section 4.2 of the SmPC.

In addition, the presented results for the proposed BroPair Spiromax low-strength combination (FS MDPI 50/12.5 mcg) were not compelling. The low-strength combination did not show a statistically significant improvement over the low-strength mono-product for any of the symptom-related endpoints in Study FSS-AS-301 and thus a clear benefit for symptoms or asthma control was not considered to be shown; and was thus withdrawn from the dossier.

A favourable clinical effect was demonstrated only for the mid- and high-strength combination (FS MDPI 100/12.5 mcg and FS MDPI 200/12.5 mcg, respectively) in the following indication:

'BroPair Spiromax is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonists.'

Taking into account the well-established safety profile of fluticasone propionate and salmeterol, the six-month long-term safety study (FSS-AS-305) adequately assessed the safety of BroPair Spiromax. Based on the safety results presented from this long-term safety study, there is currently no trend to suggest a negative benefit risk for safety. The overall safety profile of the BroPair Spiromax medium and high ICS dose strengths (FS MDPI 100/12.5 mcg and FS MDPI 200/12.5 mcg, respectively) in the asthma population investigated was comparable to the one previously established in asthma patients. Overall, the main ADRs that have been observed are known class effects of inhaled products including ICS and LABA.

3.7.2. Balance of benefits and risks

Generally, for a new controller treatment the preferred endpoint is exacerbations. Measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect. However, the efficacy of fluticasone propionate and salmeterol is well-recognised and the efficacy results for the mid- and high strengths (FS MDPI 100/12.5 mcg and FS MDPI 200/12.5 mcg, respectively), as demonstrated in the phase 3 pivotal studies FSS-AS-301 and FSS-AS-30017, were clinically significant and relevant. In addition, the overall safety profile of BroPair Spiromax was comparable to the one previously established in asthma patients. Overall, the benefit of BroPair Spiromax mid- and high strengths (FS MDPI 100/12.5 mcg and FS MDPI 200/12.5 mcg, respectively) outweighs the risk in patients with asthma.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The B/R of BroPair Spiromax mid- and high strengths (FS MDPI 100/12.5 mcg and FS MDPI 200/12.5 mcg, respectively) is positive for the regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β_2 agonists.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of BroPair Spiromax is favourable in the following indication:

BroPair Spiromax is indicated in the regular treatment of asthma in adults and adolescents aged 12 years and older not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2 agonists.

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 Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

The applicant indicated the active substances salmeterol/fluticasone propionate furoate contained in the above medicinal product to be considered as a known active substance.