Clinical trial results:
A 12-Week Dose-ranging Study to Evaluate the Efficacy and Safety of Fp Spiromax® (Fluticasone Propionate Inhalation Powder) Administered Orally Twice Daily compared with Placebo in Adolescent and Adult Subjects with Severe Persistent Asthma Uncontrolled on High dose Inhaled Corticosteroid Therapy

Summary

EudraCT number	2010-023601-35
Trial protocol	ES HU BG BE GB DE PL GR
Global end of trial date	09 October 2013

Results information

Result version number	v1 (current)
This version publication date	25 September 2016
First version publication date	25 September 2016

Trial information

Trial identification

Sponsor protocol code	FpS-AS-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01576718
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	41 Moores Road, Frazer, Pennsylvania, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 001 215-591-3000,
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 001 215-591-3000,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the dose response, efficacy and safety of 4 different doses of fluticasone propionate (50, 100, 200, and 400mcg) delivered as Fluticasone Spiromax® Inhalation Powder (Fp Spiromax) when administered twice daily in subjects 12 years of age and older with severe persistent asthma who are uncontrolled on high dose ICS therapy.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314; European Union [EU] Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use).
Written and/or oral information about the study was provided to all subjects in a language understandable by the subjects. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each subject before any study procedures or assessments were done. It was explained to the subjects that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each subject’s willingness to participate in the study was documented in writing in a consent form that was signed by the subject with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the subjects.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	30 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 64
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 150
Country: Number of subjects enrolled	Bulgaria: 49
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Hungary: 72
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	New Zealand: 1

Country: Number of subjects enrolled	United States: 444
Country: Number of subjects enrolled	Romania: 29
Country: Number of subjects enrolled	Serbia: 2
Worldwide total number of subjects	889
EEA total number of subjects	436

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	25
Adults (18-64 years)	756
From 65 to 84 years	108
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1238 subjects with asthma at 180 centers were screened for enrollment. 889 subjects met entry criteria and were enrolled into the run-in period of the study. Of the 349 subjects who were not enrolled, 337 were excluded on the basis of inclusion/exclusion criteria, 5 subjects withdrew consent, and for 6 the reason given was "other".

Pre-assignment period milestones

Number of subjects started	889
Number of subjects completed	640

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 17
Reason: Number of subjects	Inclusion criteria not met/Exclusion criteria met: 49
Reason: Number of subjects	Randomization criteria not met: 166
Reason: Number of subjects	Lost to follow-up: 2
Reason: Number of subjects	Not specified: 15

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The run-in period of this study was conducted in a single-blind manner (subject blinded) with respect to the placebo MDPI treatment. The treatment period of this study was conducted in a double-blind manner (investigator and subject blinded) with respect to Fp MDPI and placebo MDPI. FLOVENT DISKUS was administered in an open-label manner.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fp MDPI 50 mcg

Arm description:

Fluticasone propionate (Fp) 50 mcg per dose twice a day (for a total daily dose of 100 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Fp SPIROMAX® Inhalation Powder
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate multidose dry powder inhaler 50 mcg in the morning and evening for a total daily dose of 100 mcg. This medication was part of the double-blind study.

Investigational medicinal product name	albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

A short-acting β2-adrenergic agonists (SABA), albuterol/salbutamol HFA MDI, was provided to be used as needed for the relief of asthma symptoms during both the run-in and treatment periods (to replace the subject's current rescue medication).

Arm title	Fp MDPI 100 mcg

Arm description:

Fluticasone propionate (Fp) 100 mcg per dose twice a day (for a total daily dose of 200 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).
During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Fp SPIROMAX® Inhalation Powder
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate multidose dry powder inhaler 100 mcg in the morning and evening for a total daily dose of 200 mcg. This medication was part of the double-blind study.

Investigational medicinal product name	albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

A short-acting β2-adrenergic agonists (SABA), albuterol/salbutamol HFA MDI, was provided to be used as needed for the relief of asthma symptoms during both the run-in and treatment periods (to replace the subject's current rescue medication).

Arm title	Fp MDPI 200 mcg

Arm description:

Fluticasone propionate (Fp) 200 mcg per dose twice a day (for a total daily dose of 400 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Fp SPIROMAX® Inhalation Powder
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate multidose dry powder inhaler 200 mcg in the morning and evening for a total daily dose of 400 mcg. This medication was part of the double-blind study.

Investigational medicinal product name	albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

A short-acting β2-adrenergic agonists (SABA), albuterol/salbutamol HFA MDI, was provided to be used as needed for the relief of asthma symptoms during both the run-in and treatment periods (to replace the subject's current rescue medication).

Arm title	Fp MDPI 400 mcg

Arm description:

Fluticasone propionate (Fp) 400 mcg per dose twice a day (for a total daily dose of 800 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Fp SPIROMAX® Inhalation Powder
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate multidose dry powder inhaler 400 mcg in the morning and evening for a total daily dose of 800 mcg. This medication was part of the double-blind study.

Investigational medicinal product name	albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

A short-acting β2-adrenergic agonists (SABA), albuterol/salbutamol HFA MDI, was provided to be used as needed for the relief of asthma symptoms during both the run-in and treatment periods (to replace the subject's current rescue medication).

Arm title	Placebo MDPI

Arm description:

Placebo twice a day using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo multidose dry powder inhaler in the morning and evening. Placebo MDPI was provided in devices identical in appearance to Fp MDPI and was part of the double-blind study.

Investigational medicinal product name	albuterol/salbutamol
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

A short-acting β2-adrenergic agonists (SABA), albuterol/salbutamol HFA MDI, was provided to be used as needed for the relief of asthma symptoms during both the run-in and treatment periods (to replace the subject's current rescue medication).

Arm title	Flovent Diskus

Arm description:

Fluticasone propionate (Fp) 250 mcg per dose twice a day (for a total daily dose of 500 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in an open-label manner.
During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Flovent Diskus
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

250 mcg

Investigational medicinal product name	albuterol/salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

A short-acting β2-adrenergic agonists (SABA), albuterol/salbutamol HFA MDI, was provided to be used as needed for the relief of asthma symptoms during both the run-in and treatment periods (to replace the subject's current rescue medication).

Number of subjects in period 1[1]	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg
Started	107	107	106
Safety population	107	107	106
Efficacy population (Full Analysis Set)	107	106	102
Completed	82	87	75
Not completed	25	20	31
Consent withdrawn by subject	1	1	-
Physician decision	1	1	1
Met stopping criteria	16	13	19
Noncompliance to study medication	-	-	-
Adverse event, non-fatal	1	1	1
Sponsor requested subject to be withdrawn	1	-	-
Lost to follow-up	-	-	-
Protocol deviation	5	4	10

Number of subjects in period 1[1]	Fp MDPI 400 mcg	Placebo MDPI	Flovent Diskus
Started	107	106	107
Safety population	107	106	106
Efficacy population (Full Analysis Set)	107	105	103
Completed	80	58	77
Not completed	27	48	30
Consent withdrawn by subject	2	4	2
Physician decision	1	-	-
Met stopping criteria	16	33	15
Noncompliance to study medication	-	1	1
Adverse event, non-fatal	1	1	-
Sponsor requested subject to be withdrawn	-	1	-
Lost to follow-up	1	-	-
Protocol deviation	6	8	12

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 889 patients were enrolled and received run-in placebo; 640 patients were randomized into the Treatment Period for which baseline characteristics are reported.

Baseline characteristics

Reporting groups	
Reporting group title	Fp MDPI 50 mcg

Reporting group description:

Fluticasone propionate (Fp) 50 mcg per dose twice a day (for a total daily dose of 100 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 100 mcg

Reporting group description:

Fluticasone propionate (Fp) 100 mcg per dose twice a day (for a total daily dose of 200 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).
During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 200 mcg

Reporting group description:

Fluticasone propionate (Fp) 200 mcg per dose twice a day (for a total daily dose of 400 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 400 mcg

Reporting group description:

Fluticasone propionate (Fp) 400 mcg per dose twice a day (for a total daily dose of 800 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Placebo MDPI

Reporting group description:

Placebo twice a day using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Flovent Diskus

Reporting group description:

Fluticasone propionate (Fp) 250 mcg per dose twice a day (for a total daily dose of 500 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in an open-label manner.
During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg
Number of subjects	107	107	106

Age categorical Units: Subjects			
Adolescents (12-17 years)	2	3	1
Adults (18-64 years)	94	99	90
From 65-84 years	11	5	15
Age continuous Units: years			
arithmetic mean	47.9	48.7	47.7
standard deviation	± 14.59	± 12.48	± 14.18
Gender categorical Units: Subjects			
Female	63	55	66
Male	44	52	40
Race Units: Subjects			
White	96	94	93
Black	9	12	12
Asian	1	1	1
American Indian or Alaskan Native	0	0	0
Pacific Islander	1	0	0
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	5	7	8
Not Hispanic or Latino	102	100	98
Weight Units: kg			
arithmetic mean	86.7	86.6	84.4
standard deviation	± 23.73	± 22.9	± 21.89
Height Units: cm			
arithmetic mean	169.4	168.7	168.4
standard deviation	± 13.04	± 9.14	± 7.86
Body Mass Index Units: kg/m^2			
arithmetic mean	31.3	30.4	29.8
standard deviation	± 17.88	± 7.6	± 8.12
Forced Expiratory Volume in 1 Second (FEV1) Units: liters			
arithmetic mean	2.108	2.031	1.999
standard deviation	± 0.662	± 0.551	± 0.525
% Predicted Expiratory Volume In 1 Second Units: percent predicted FEV1			
arithmetic mean	63.7	63.1	63.4
standard deviation	± 10.9	± 9.5	± 12.1
Qualifying Airway Reversibility			
Patients demonstrated a ≥12% reversibility of FEV1 within 30 minutes following 2-4 inhalations of albuterol/salbutamol inhalation aerosol at the screening visit. If subjects failed to demonstrate an increase in FEV1 ≥12% then subjects were not eligible for the study; however, based on investigator judgment, they were allowed to retest once within 7 days. Reversibility values of 11.50 through 11.99% were rounded to 12%. Documented historical reversibility of ≥12 % within 1 year was accepted.			

Units: percentage increase in FEV1			
arithmetic mean	31.6	27.3	30.4
standard deviation	± 22.4	± 14.7	± 25.2

Reporting group values	Fp MDPI 400 mcg	Placebo MDPI	Flovent Diskus
Number of subjects	107	106	107
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	1	1	1
Adults (18-64 years)	90	94	96
From 65-84 years	16	11	10
Age continuous			
Units: years			
arithmetic mean	50.9	49.8	49.2
standard deviation	± 13.32	± 12.87	± 13.26
Gender categorical			
Units: Subjects			
Female	72	65	58
Male	35	41	49
Race			
Units: Subjects			
White	91	96	95
Black	13	8	11
Asian	2	2	0
American Indian or Alaskan Native	0	0	1
Pacific Islander	0	0	0
Other	1	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	12	6	9
Not Hispanic or Latino	95	100	98
Weight			
Units: kg			
arithmetic mean	84.4	86.2	83.3
standard deviation	± 20.56	± 25.19	± 16.76
Height			
Units: cm			
arithmetic mean	167.4	168.1	168
standard deviation	± 9.67	± 8.57	± 8.33
Body Mass Index			
Units: kg/m^2			
arithmetic mean	30.1	30.5	29.6
standard deviation	± 6.81	± 8.83	± 6.03
Forced Expiratory Volume in 1 Second (FEV1)			
Units: liters			
arithmetic mean	2.016	1.984	1.955
standard deviation	± 0.636	± 0.565	± 0.529
% Predicted Expiratory Volume In 1 Second			
Units: percent predicted FEV1			
arithmetic mean	65.3	63.1	62.5

standard deviation	± 11.4	± 10	± 12.1
Qualifying Airway Reversibility			
Patients demonstrated a ≥12% reversibility of FEV1 within 30 minutes following 2-4 inhalations of albuterol/salbutamol inhalation aerosol at the screening visit. If subjects failed to demonstrate an increase in FEV1 ≥12% then subjects were not eligible for the study; however, based on investigator judgment, they were allowed to retest once within 7 days. Reversibility values of 11.50 through 11.99% were rounded to 12%. Documented historical reversibility of ≥12 % within 1 year was accepted.			
Units: percentage increase in FEV1			
arithmetic mean	29.1	28.9	26.8
standard deviation	± 19.5	± 19.1	± 15.7

Reporting group values	Total		
Number of subjects	640		
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	9		
Adults (18-64 years)	563		
From 65-84 years	68		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	379		
Male	261		
Race			
Units: Subjects			
White	565		
Black	65		
Asian	7		
American Indian or Alaskan Native	1		
Pacific Islander	1		
Other	1		
Ethnicity			
Units: Subjects			
Hispanic or Latino	47		
Not Hispanic or Latino	593		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Body Mass Index			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		
Forced Expiratory Volume in 1 Second (FEV1)			
Units: liters			

arithmetic mean standard deviation	- 		
% Predicted Expiratory Volume In 1 Second Units: percent predicted FEV1 arithmetic mean standard deviation	- 		
Qualifying Airway Reversibility			
Patients demonstrated a ≥12% reversibility of FEV1 within 30 minutes following 2-4 inhalations of albuterol/salbutamol inhalation aerosol at the screening visit. If subjects failed to demonstrate an increase in FEV1 ≥12% then subjects were not eligible for the study; however, based on investigator judgment, they were allowed to retest once within 7 days. Reversibility values of 11.50 through 11.99% were rounded to 12%. Documented historical reversibility of ≥12 % within 1 year was accepted.			
Units: percentage increase in FEV1 arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Fp MDPI 50 mcg

Reporting group description:

Fluticasone propionate (Fp) 50 mcg per dose twice a day (for a total daily dose of 100 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 100 mcg

Reporting group description:

Fluticasone propionate (Fp) 100 mcg per dose twice a day (for a total daily dose of 200 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).
During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 200 mcg

Reporting group description:

Fluticasone propionate (Fp) 200 mcg per dose twice a day (for a total daily dose of 400 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 400 mcg

Reporting group description:

Fluticasone propionate (Fp) 400 mcg per dose twice a day (for a total daily dose of 800 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Placebo MDPI

Reporting group description:

Placebo twice a day using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Flovent Diskus

Reporting group description:

Fluticasone propionate (Fp) 250 mcg per dose twice a day (for a total daily dose of 500 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in an open-label manner.
During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Primary: Change From Baseline In Trough (Morning Predose And Pre-Rescue Bronchodilator) Forced Expiratory Volume In 1 Second (FEV1) Over The 12-Week Treatment Period

End point title	Change From Baseline In Trough (Morning Predose And Pre-Rescue Bronchodilator) Forced Expiratory Volume In 1 Second (FEV1) Over The 12-Week Treatment Period

End point description:

Trough FEV1 was measured electronically by spirometry at morning (AM) investigational site visits, before administration of the AM dose of study drug, and before albuterol/salbutamol administration. The highest FEV1 value from 3 acceptable and 2 reproducible maneuvers was used. All FEV1 data were submitted to a central reading center for evaluation.

The p-values for the treatment comparisons to placebo are from an MMRM model excluding FLOVENT DISKUS data: change from baseline = baseline FEV1 + sex + age + treatment + visit + treatment*visit with an unstructured covariance matrix assumed.

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose), Weeks 1, 2, 3, 4, 6, 8, 10 and 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104[1]	102[2]	97[3]	103[4]
Units: liters				
least squares mean (standard error)	0.059 (± 0.0269)	0.101 (± 0.0268)	0.109 (± 0.0278)	0.125 (± 0.0274)

Notes:

[1] - Full analysis set

[2] - Full analysis set

[3] - Full analysis set

[4] - Full analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[5]	0[6]		
Units: liters				
least squares mean (standard error)	0.053 (± 0.0283)	()		

Notes:

[5] - Full analysis set

[6] - Flovent Diskus data was used for confirmatory and exploratory endpoints and not in this endpoint.

Statistical analyses

Statistical analysis title	Change in FEV1 Linear Trend Test

Statistical analysis description:

A linear in log-dose trend contrast was constructed to evaluate the time-averaged dose-response trend, where the logarithm of dose was defined as log(dose+1) to accommodate the case of a zero dose (placebo). A fixed-sequence testing procedure was employed to control the overall Type I error rate at the 0.05 level. Specifically, the 2-sided linear in log-dose time-averaged trend test was first performed at the 0.05 level of significance.

Comparison groups	Fp MDPI 50 mcg v Fp MDPI 100 mcg v Fp MDPI 200 mcg v Fp MDPI 400 mcg v Placebo MDPI

Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0604 [7]
Method	Regression, Linear

Notes:

[7] - If the Fp MDPI showed a significantly positive trend, then contrasts for pairwise comparisons of each Fp MDPI dose versus placebo were done in the sequence of highest to lowest Fp MDPI dose.

Statistical analysis title	Change in FEV1: Fp 400 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 400 mcg v Placebo MDPI
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0637 [8]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	0.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.149

Notes:

[8] - Significance at the 0.05 level

Statistical analysis title	Change in FEV1: Fp 200 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1585 [9]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.133

Notes:

[9] - Significance at the 0.05 level

Statistical analysis title	Change in FEV1: Fp 100 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2221 [10]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.124

Notes:

[10] - Significance at the 0.05 level

Statistical analysis title	Change in FEV1: Fp 50 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 50 mcg v Placebo MDPI
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8694 [11]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.083

Notes:

[11] - Significance at the 0.05 level

Secondary: Change From Baseline In Weekly Average Of Daily Trough (Predose And Pre-Rescue Bronchodilator) Morning Peak Expiratory Flow (PEF) Over The 12-Week Treatment Period

End point title	Change From Baseline In Weekly Average Of Daily Trough (Predose And Pre-Rescue Bronchodilator) Morning Peak Expiratory Flow (PEF) Over The 12-Week Treatment Period

End point description:

Peak expiratory flow was determined in the AM and in the PM, before administration of study or rescue medications using a handheld electronic peak flow meter. The highest value of triplicate measurements obtained was recorded by the subject’s diary device.
On mornings for which a treatment visit was scheduled (TV1 through TV9), the PEF was measured and recorded at the investigational site visit.
Baseline trough AM PEF was defined as the average of recorded (nonmissing) trough AM PEF assessments over the 7 days directly preceding first study drug intake.

The p-values for the treatment comparisons to placebo are from an MMRM model excluding FLOVENT DISKUS data: change from baseline = baseline PEF + sex + age + treatment + visit + treatment*visit with an unstructured covariance matrix assumed.

End point type	Secondary

End point timeframe:

Baseline (Days -6 to Day 1 pre-dose), Weeks 1, 2, 3, 4, 6, 8, 10 and 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	101[12]	101[13]	96[14]	101[15]
Units: liters/minute				
least squares mean (standard error)	10.48 (± 4.299)	9.34 (± 4.245)	10.03 (± 4.42)	9.61 (± 4.307)

Notes:

[12] - Full analysis set

[13] - Full analysis set

[14] - Full analysis set

[15] - Full analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[16]	0[17]		
Units: liters/minute				
least squares mean (standard error)	2.24 (± 4.507)	()		

Notes:

[16] - Full analysis set

[17] - Flovent Diskus data was used for confirmatory and exploratory endpoints and not in this endpoint.

Statistical analyses

Statistical analysis title	Change in AM PEF Linear Trend Test

Statistical analysis description:

A linear in log-dose trend contrast was constructed to evaluate the time-averaged dose-response trend, where the logarithm of dose was defined as log(dose+1) to accommodate the case of a zero dose (placebo). A fixed-sequence testing procedure was employed to control the overall Type I error rate at the 0.05 level. Specifically, the 2-sided linear in log-dose time-averaged trend test was first performed at the 0.05 level of significance.

Comparison groups	Fp MDPI 50 mcg v Fp MDPI 100 mcg v Fp MDPI 200 mcg v Fp MDPI 400 mcg v Placebo MDPI
Number of subjects included in analysis	497
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1512 [18]
Method	Regression, Linear

Notes:

[18] - If the Fp MDPI showed a significantly positive trend, then contrasts for pairwise comparisons of each Fp MDPI dose versus placebo were done in the sequence of highest to lowest Fp MDPI dose.

Statistical analysis title	Change in AM PEF: Fp 400 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for

comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 400 mcg v Placebo MDPI
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2361 [19]
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	7.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.83
upper limit	19.56

Notes:

[19] - Significance at the 0.05 level

Statistical analysis title	Change in AM PEF: Fp 200 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2169 [20]
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	7.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.59
upper limit	20.15

Notes:

[20] - Significance at the 0.05 level

Statistical analysis title	Change in AM PEF: Fp 100 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2523 [21]
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	7.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.07
upper limit	19.26

Notes:

[21] - Significance at the 0.05 level

Statistical analysis title	Change in AM PEF: Fp 50 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 50 mcg v Placebo MDPI
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1858 [22]
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	8.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.98
upper limit	20.45

Notes:

[22] - Significance at the 0.05 level

Secondary: Change From Baseline In Weekly Average Of Daily Trough (Predose And Pre-Rescue Bronchodilator) Evening Peak Expiratory Flow (PEF) Over The 12-Week Treatment Period

End point title	Change From Baseline In Weekly Average Of Daily Trough (Predose And Pre-Rescue Bronchodilator) Evening Peak Expiratory Flow (PEF) Over The 12-Week Treatment Period

End point description:

Peak expiratory flow was determined in the AM and in the PM, before administration of study or rescue medications using a handheld electronic peak flow meter. The highest value of triplicate measurements obtained was recorded by the subject’s diary device.
PM PEF baseline was defined as the average of recorded (nonmissing) PM PEF assessments over the 7 days directly preceding first study drug intake.
The p-values for the treatment comparisons to placebo are from an MMRM model excluding FLOVENT DISKUS data: change from baseline = baseline PEF + sex + age + treatment + visit + treatment*visit with an unstructured covariance matrix assumed.

End point type	Secondary

End point timeframe:

Baseline (Days -6 to Day 1 pre-dose), Weeks 1, 2, 3, 4, 6, 8, 10 and 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	103[23]	99[24]	96[25]	102[26]
Units: liters/minute				
least squares mean (standard error)	3.81 (± 4.183)	6.41 (± 4.209)	7.45 (± 4.335)	10.97 (± 4.208)

Notes:

[23] - Full analysis set

[24] - Full analysis set

[25] - Full analysis set

[26] - Full analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96[27]	0[28]		
Units: liters/minute				
least squares mean (standard error)	3.42 (± 4.462)	()		

Notes:

[27] - Full analysis set

[28] - Flovent Diskus data was used for confirmatory and exploratory endpoints and not in this endpoint.

Statistical analyses

Statistical analysis title	Change in PM PEF Linear Trend Test

Statistical analysis description:

A linear in log-dose trend contrast was constructed to evaluate the time-averaged dose-response trend, where the logarithm of dose was defined as log(dose+1) to accommodate the case of a zero dose (placebo). A fixed-sequence testing procedure was employed to control the overall Type I error rate at the 0.05 level. Specifically, the 2-sided linear in log-dose time-averaged trend test was first performed at the 0.05 level of significance.

Comparison groups	Fp MDPI 50 mcg v Fp MDPI 100 mcg v Fp MDPI 200 mcg v Fp MDPI 400 mcg v Placebo MDPI
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2879 [29]
Method	Regression, Linear

Notes:

[29] - If the Fp MDPI showed a significantly positive trend, then contrasts for pairwise comparisons of each Fp MDPI dose versus placebo were done in the sequence of highest to lowest Fp MDPI dose.

Statistical analysis title	Change in PM PEF: Fp 400 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 400 mcg v Placebo MDPI
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2166 [30]
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	7.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.45
upper limit	19.56

Notes:

[30] - Significance at the 0.05 level

Statistical analysis title	Change in PM PEF: Fp 200 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5167 [31]
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	4.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.17
upper limit	16.23

Notes:

[31] - Significance at the 0.05 level

Statistical analysis title	Change in PM PEF: Fp 100 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6258 [32]
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	2.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.06
upper limit	15.05

Notes:

[32] - Significance at the 0.05 level

Statistical analysis title	Change in PM PEF: Fp 50 - Placebo

Statistical analysis description:

No explicit structure was assumed for the covariance among the repeated measures. Analyses for comparison of Fp MDPI to placebo did not contain FLOVENT DISKUS data.

Comparison groups	Fp MDPI 50 mcg v Placebo MDPI
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9487 [33]
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.6
upper limit	12.39

Notes:

[33] - Significance at the 0.05 level

Secondary: The Kaplan-Meier Estimate Of The Probability Of Remaining In The Study At Week 12

End point title	The Kaplan-Meier Estimate Of The Probability Of Remaining In The Study At Week 12

End point description:

The analysis of probability of remaining in the study at Week 12 used the time to patient withdrawal for worsening asthma. Worsening asthma was defined as:
- clinic visit FEV1 below the FEV1 stability limit value calculated on Day 1.
-any 7-day run-in or treatment window (using information from the patient diary), the subject experienced:
3 or more days in which the highest PEF has fallen below the PEF stability limit calculated on Day 1
3 or more days in which ≥12 inhalations/day of albuterol/salbutamol was used
2 or more days in which the subject experienced a nighttime asthma symptom score of >2
- clinical asthma exacerbation, defined as worsening asthma requiring any treatment other than study drug or rescue albuterol/salbutamol including the use of systemic corticosteroids and/or ER visit or hospitalization.
Patients who had withdrawn due to reasons other than worsening asthma
were right-censored at the date of last assessment

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107[34]	106[35]	102[36]	107[37]
Units: probability				
number (confidence interval 95%)	0.6872 (0.5891 to 0.7665)	0.633 (0.5307 to 0.7188)	0.5852 (0.4796 to 0.6766)	0.6109 (0.5093 to 0.6977)

Notes:

[34] - Full analysis set

[35] - Full analysis set

[36] - Full analysis set

[37] - Full analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[38]	103[39]		
Units: probability				
number (confidence interval 95%)	0.4722 (0.3712 to 0.5665)	0.5657 (0.4617 to 0.6571)		

Notes:

[38] - Full analysis set

[39] - Full analysis set

Statistical analyses

Statistical analysis title	Probability 12 Weeks: Fp 400 - Placebo
Comparison groups	Fp MDPI 400 mcg v Placebo MDPI
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0341 [40]
Method	Logrank

Notes:

[40] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: Fp 200 - Placebo
Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 [41]
Method	Logrank

Notes:

[41] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: Fp 100 - Placebo
Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058 [42]
Method	Logrank

Notes:

[42] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: Fp 50 - Placebo
Comparison groups	Fp MDPI 50 mcg v Placebo MDPI

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018 [43]
Method	Logrank

Notes:

[43] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FLOVENT DISKUS - Placebo
Comparison groups	Flovent Diskus v Placebo MDPI
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1006 [44]
Method	Logrank

Notes:

[44] - Significance level of 0.05.

Secondary: Change From Baseline In The Percentage Of Rescue-Free 24-Hour Periods

End point title	Change From Baseline In The Percentage Of Rescue-Free 24-Hour Periods

End point description:

The change from baseline in the percentage of rescue-free 24-hour periods was analyzed with a marginal (also called population averaged) logistic model, with the response being the proportion of rescue-free 24-hour periods. The model included 2 time points of measurement for each subject: the baseline (the last 7 days before the treatment period) and the treatment period. The model contained covariates for sex, age, and treatment. Rescue-free days were as indicated in patient diaries.

Data values are estimated means.

End point type	Secondary

End point timeframe:

Baseline (Day -6 to Day 1 predose), Treatment (Day 1 to Week 12)

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96[45]	90[46]	91[47]	99[48]
Units: percentage of total 24 hour periods				
arithmetic mean (standard error)	22.78 (± 4.016)	26.41 (± 4.013)	16.18 (± 3.662)	28.05 (± 3.951)

Notes:

[45] - Full analysis set

[46] - Full analysis set

[47] - Full analysis set

[48] - Full analysis set

End point values	Placebo MDPI	Flovent Diskus		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[49]	95[50]		
Units: percentage of total 24 hour periods				
arithmetic mean (standard error)	27.15 (± 4.475)	15.87 (± 3.75)		

Notes:

[49] - Full analysis set

[50] - Full analysis set

Statistical analyses

Statistical analysis title	% Change in Rescue-Free 24 Hrs: Fp 400 - Placebo

Statistical analysis description:

Estimates computed from a generalized linear logistic model with gender and age as covariates and allows correlation between estimates on
the same subject. Interpretation of the estimates is that they are the average over the population at the average level of continuous
covariate (age) averaged over discrete covariate (gender).

Comparison groups	Fp MDPI 400 mcg v Placebo MDPI
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88116 [51]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.12
upper limit	12.91

Notes:

[51] - Significance at the 0.05 level

Statistical analysis title	% Change in Rescue-Free 24 Hrs: Fp 200 - Placebo

Statistical analysis description:

Estimates computed from a generalized linear logistic model with gender and age as covariates and allows correlation between estimates on
the same subject. Interpretation of the estimates is that they are the average over the population at the average level of continuous
covariate (age) averaged over discrete covariate (gender).

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05977 [52]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-10.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.64
upper limit	0.68

Notes:

[52] - Significance at the 0.05 level

Statistical analysis title	% Change in Rescue-Free 24 Hrs: Fp 100 - Placebo

Statistical analysis description:

Estimates computed from a generalized linear logistic model with gender and age as covariates and allows correlation between estimates on
the same subject. Interpretation of the estimates is that they are the average over the population at the average level of continuous
covariate (age) averaged over discrete covariate (gender).

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.90426 [53]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.02
upper limit	11.54

Notes:

[53] - Significance at the 0.05 level

Statistical analysis title	% Change in Rescue-Free 24 Hrs: Fp 50 - Placebo

Statistical analysis description:

Estimates computed from a generalized linear logistic model with gender and age as covariates and allows correlation between estimates on
the same subject. Interpretation of the estimates is that they are the average over the population at the average level of continuous
covariate (age) averaged over discrete covariate (gender).

Comparison groups	Fp MDPI 50 mcg v Placebo MDPI
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4731 [54]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-4.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.57
upper limit	7.82

Notes:

[54] - Significance at the 0.05 level

Secondary: Area Under The Plasma Concentration-Time Curve From Time Zero To The Time Of The Last Measurable Concentration (AUC0-t)

End point title	Area Under The Plasma Concentration-Time Curve From Time Zero To The Time Of The Last Measurable Concentration (AUC0-t)[55]

End point description:

End point type	Secondary

End point timeframe:

Day 1 predose (within 10 minutes of treatment administration), and 5, 10, 15, 30, and 45 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, and 2, 4, 8, and 12 hours postdose

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK assessments not reported for placebo arm.

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[56]	16[57]	18[58]	20[59]
Units: pg*hr/mL				
arithmetic mean (standard deviation)	117.6 (± 145.79)	126.8 (± 33.73)	292 (± 162.28)	462.8 (± 262.45)

Notes:

[56] - Pharmacokinetics Analysis set

[57] - Pharmacokinetics Analysis set; two patients did not have AUC data.

[58] - Pharmacokinetics Analysis set

[59] - Pharmacokinetics Analysis set

End point values	Flovent Diskus			
Subject group type	Reporting group			
Number of subjects analysed	16[60]			
Units: pg*hr/mL				
arithmetic mean (standard deviation)	162.3 (± 74.79)			

Notes:

[60] - Pharmacokinetics Analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)[61]

End point description:

End point type	Secondary

End point timeframe:

Day 1 predose (within 10 minutes of treatment administration), and 5, 10, 15, 30, and 45 minutes, 1

hour, 1 hour 15 minutes, 1 hour 30 minutes, and 2, 4, 8, and 12 hours postdose

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK assessments not reported for placebo arm.

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[62]	16[63]	18[64]	20[65]
Units: pg/mL				
arithmetic mean (standard deviation)	19.1 (± 15.53)	26.5 (± 6.18)	55.2 (± 29.12)	83 (± 44.32)

Notes:

[62] - Pharmacokinetics Analysis set

[63] - Pharmacokinetics Analysis set; two patients did not have Cmax data

[64] - Pharmacokinetics Analysis set

[65] - Pharmacokinetics Analysis set

End point values	Flovent Diskus			
Subject group type	Reporting group			
Number of subjects analysed	16[66]			
Units: pg/mL				
arithmetic mean (standard deviation)	32.5 (± 13.92)			

Notes:

[66] - Pharmacokinetics Analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Time Of Maximum Observed Plasma Concentration (tmax)

End point title	Time Of Maximum Observed Plasma Concentration (tmax)[67]

End point description:

End point type	Secondary

End point timeframe:

Day 1 predose (within 10 minutes of treatment administration), and 5, 10, 15, 30, and 45 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, and 2, 4, 8, and 12 hours postdose

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK assessments not reported for placebo arm.

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[68]	16[69]	18[70]	20[71]
Units: hour				
arithmetic mean (standard deviation)	1 (± 0.54)	1.2 (± 1.85)	2.2 (± 3.58)	1.4 (± 2.6)

Notes:

[68] - Pharmacokinetics Analysis set

[69] - Pharmacokinetics Analysis set; two patients do not have Tmax data

[70] - Pharmacokinetics Analysis set

[71] - Pharmacokinetics Analysis set

End point values	Flovent Diskus			
Subject group type	Reporting group			
Number of subjects analysed	16[72]			
Units: hour				
arithmetic mean (standard deviation)	1.8 (± 2.75)			

Notes:

[72] - Pharmacokinetics Analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with Treatment-Emergent Adverse Experiences (TEAE) During the Treatment Period

End point title	Patients with Treatment-Emergent Adverse Experiences (TEAE) During the Treatment Period

End point description:

An adverse event was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents normal daily activities. Relationship of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107[73]	107[74]	106[75]	107[76]
Units: patients				
Any adverse event	31	27	34	41
Severe AE	3	1	1	1
Treatment-related AE	4	1	6	9
Deaths	0	0	0	0
Other serious AE	1	1	1	0
Withdrawn from treatment due to AE	1	1	1	1

Notes:

[73] - Safety analysis set

[74] - Safety analysis set

[75] - Safety analysis set

[76] - Safety analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[77]	106[78]		
Units: patients				
Any adverse event	33	27		
Severe AE	1	0		
Treatment-related AE	5	2		
Deaths	0	0		
Other serious AE	1	0		
Withdrawn from treatment due to AE	1	0		

Notes:

[77] - Safety analysis set

[78] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with Positive Swab Test Results for Oral Candidiasis

End point title	Patients with Positive Swab Test Results for Oral Candidiasis

End point description:

Oropharyngeal examinations for visual evidence of oral candidiasis were conducted at each visit. Any visual evidence of oral candidiasis during the oropharyngeal exam was evaluated by obtaining and analyzing a swab of the suspect area. This outcomes indicates who many patients had positive swab test results. The total number of patients who had oropharyngeal exams at each timepoint are specified in the timepoint field.

Appropriate therapy was to be initiated immediately at the discretion of the investigator and was not to be delayed for culture confirmation. Subjects with a culture-positive infection could continue participation in the study on appropriate anti-infective therapy, provided this therapy was not prohibited by the protocol.

End point type	Secondary

End point timeframe:

Screening (Days -21 to -14), Randomization (Day 1), Weeks 1, 2, 3, 4, 6, 8, 10, 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107[79]	107[80]	106[81]	107[82]
Units: patients				
Screening (n=107, 106, 106, 107, 106, 104)	0	0	0	0
Day 1 (n=107. 107, 106, 107, 106, 106)	0	0	1	0
Week 1 (n=102, 103, 98, 97, 96, 99)	0	0	0	0
Week 2 (n=99, 101, 94, 95, 84, 92)	0	0	1	2
Week 3 (n=91, 98, 92, 93, 80, 87)	0	0	0	4
Week 4 (n=91, 95, 88, 87, 75, 87)	1	0	1	1
Week 6 (n=86, 92, 86, 86, 68, 85)	0	0	0	1

Week 8 (n=83, 90, 81, 83, 64, 82)	0	0	1	0
Week 10 (n=83, 87, 77, 82, 60, 79)	0	0	0	1
Week 12 (n=104, 104, 103, 106, 102, 100)	0	0	0	1

Notes:

[79] - Safety Analysis set

[80] - Safety Analysis set

[81] - Safety Analysis set

[82] - Safety Analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[83]	106[84]		
Units: patients				
Screening (n=107, 106, 106, 107, 106, 104)	0	0		
Day 1 (n=107. 107, 106, 107, 106, 106)	1	1		
Week 1 (n=102, 103, 98, 97, 96, 99)	1	1		
Week 2 (n=99, 101, 94, 95, 84, 92)	0	0		
Week 3 (n=91, 98, 92, 93, 80, 87)	0	0		
Week 4 (n=91, 95, 88, 87, 75, 87)	0	0		
Week 6 (n=86, 92, 86, 86, 68, 85)	0	0		
Week 8 (n=83, 90, 81, 83, 64, 82)	0	1		
Week 10 (n=83, 87, 77, 82, 60, 79)	0	0		
Week 12 (n=104, 104, 103, 106, 102, 100)	0	1		

Notes:

[83] - Safety Analysis set

[84] - Safety Analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: 24-Hour Urinary Cortisol Excretion at Baseline, Week 12 and Endpoint

End point title	24-Hour Urinary Cortisol Excretion at Baseline, Week 12 and Endpoint

End point description:

24-hour urinary cortisol excretion was determined from 24-hour pooled-urine samples; urine was refrigerated until return to the investigational site after each 24-hour collection period. Urine was collected within 7 days of Day 1 and within 7 days of Week 12. Urine cortisol sample collection was not required at endpoint visit for subjects who terminated early from the study.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 12, Endpoint

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[85]	72[86]	56[87]	68[88]
Units: nmol/day				
arithmetic mean (standard deviation)				
Baseline (n=62, 70, 55, 68, 41, 59)	65.3 (± 42.69)	63.8 (± 44.7)	66.6 (± 45.53)	57.4 (± 34.68)
Week 12 (n=61, 70, 53, 65, 38, 57)	71.8 (± 48.37)	61.5 (± 45.73)	66.8 (± 53.96)	46.2 (± 38.67)
Endpoint (n=62, 70, 55, 68, 41, 59)	71 (± 48.31)	61.5 (± 45.73)	65.8 (± 53.33)	45 (± 38.33)

Notes:

[85] - Urine Cortisol Analysis set

[86] - Urine Cortisol Analysis set

[87] - Urine Cortisol Analysis set

[88] - Urine Cortisol Analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43[89]	59[90]		
Units: nmol/day				
arithmetic mean (standard deviation)				
Baseline (n=62, 70, 55, 68, 41, 59)	74.3 (± 43.54)	66.2 (± 42.68)		
Week 12 (n=61, 70, 53, 65, 38, 57)	69.2 (± 49.56)	58.5 (± 43.75)		
Endpoint (n=62, 70, 55, 68, 41, 59)	74.4 (± 54.97)	58.4 (± 43.49)		

Notes:

[89] - Urine Cortisol Analysis set

[90] - Urine Cortisol Analysis set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline In Trough (Morning Predose And Pre-Rescue Bronchodilator) Forced Expiratory Volume In 1 Second (FEV1) Over The 12-Week Treatment Period (Including the Flovent Diskus treatment arm)

End point title	Change From Baseline In Trough (Morning Predose And Pre-Rescue Bronchodilator) Forced Expiratory Volume In 1 Second (FEV1) Over The 12-Week Treatment Period (Including the Flovent Diskus treatment arm)

End point description:

Peak expiratory flow was determined in the AM and in the PM, before administration of study or rescue medications using a handheld electronic peak flow meter. The highest value of triplicate measurements obtained was recorded by the subject's diary device.
On mornings for which a treatment visit was scheduled (TV1 through TV9), the PEF was measured and recorded at the investigational site visit.
Baseline trough AM PEF was defined as the average of recorded (nonmissing) trough AM PEF assessments over the 7 days directly preceding first study drug intake.

The p-values for the treatment comparisons to Flovent Diskus are from an MMRM model which includes data from all treatments: change from baseline = baseline PEF + sex + age + treatment + visit + treatment*visit with an unstructured covariance matrix assumed.

End point type	Other pre-specified

End point timeframe:

Baseline (Day 1 pre-dose), Weeks 1, 2, 3, 4, 6, 8, 10 and 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104[91]	102[92]	97[93]	103[94]
Units: liters				
least squares mean (standard error)	0.063 (± 0.027)	0.102 (± 0.0269)	0.113 (± 0.0279)	0.129 (± 0.0274)

Notes:

[91] - Full analysis set

[92] - Full analysis set

[93] - Full analysis set

[94] - Full analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[95]	100[96]		
Units: liters				
least squares mean (standard error)	0.057 (± 0.0284)	0.11 (± 0.0274)		

Notes:

[95] - Full analysis set

[96] - Full analysis set

Statistical analyses

Statistical analysis title	Change in FEV1: Fp 400 - Flovent Diskus
Comparison groups	Fp MDPI 400 mcg v Flovent Diskus
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6161
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.057
upper limit	0.096

Statistical analysis title	Change in FEV1: Fp 200 - Flovent Diskus
Comparison groups	Fp MDPI 200 mcg v Flovent Diskus

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9245
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.973
upper limit	0.08

Statistical analysis title	Change in FEV1: Fp 100 - Flovent Diskus
Comparison groups	Fp MDPI 100 mcg v Flovent Diskus
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8434
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.083
upper limit	0.068

Statistical analysis title	Change in FEV1: Fp 50 - Flovent Diskus
Comparison groups	Fp MDPI 50 mcg v Flovent Diskus
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2241
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.122
upper limit	0.029

Statistical analysis title	Change in FEV1: Placebo - Flovent Diskus

Comparison groups	Placebo MDPI v Flovent Diskus
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1822
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.025

Other pre-specified: Change From Baseline In Weekly Average Of Daily Trough (Predose And Pre-Rescue Bronchodilator) Morning Peak Expiratory Flow (PEF) Over The 12-Week Treatment Period (Including the Flovent Diskus treatment arm)

End point title	Change From Baseline In Weekly Average Of Daily Trough (Predose And Pre-Rescue Bronchodilator) Morning Peak Expiratory Flow (PEF) Over The 12-Week Treatment Period (Including the Flovent Diskus treatment arm)

End point description:

Peak expiratory flow was determined in the AM and in the PM, before administration of study or rescue medications using a handheld electronic peak flow meter. The highest value of triplicate measurements obtained was recorded by the subject's diary device.
On mornings for which a treatment visit was scheduled (TV1 through TV9), the PEF was measured and recorded at the investigational site visit.
Baseline trough AM PEF was defined as the average of recorded (nonmissing) trough AM PEF assessments over the 7 days directly preceding first study drug intake.

The p-values for the treatment comparisons to Flovent Diskus are from an MMRM model that included data for all treatments: change from baseline = baseline PEF + sex + age + treatment + visit + treatment*visit with an unstructured covariance matrix assumed.

End point type	Other pre-specified

End point timeframe:

Baseline (Days -6 to Day 1 pre-dose), Weeks 1, 2, 3, 4, 6, 8, 10 and 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	101[97]	101[98]	96[99]	101[100]
Units: liters/minute				
least squares mean (standard error)	10.85 (± 4.245)	9.39 (± 4.193)	10.29 (± 4.362)	10.4 (± 4.254)

Notes:

[97] - Full analysis set

[98] - Full analysis set

[99] - Full analysis set

[100] - Full analysis set

End point values	Placebo MDPI	Flovent Diskus		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[101]	99[102]		
Units: liters/minute				
least squares mean (standard error)	2.52 (± 4.453)	15.97 (± 4.283)		

Notes:

[101] - Full analysis set

[102] - Full analysis set

Statistical analyses

Statistical analysis title	Change in AM PEF: Fp 400 - Flovent Diskus
Comparison groups	Fp MDPI 400 mcg v Flovent Diskus
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3568
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-5.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.42
upper limit	6.29

Statistical analysis title	Change in AM PEF: Fp 200 - Flovent Diskus
Comparison groups	Fp MDPI 200 mcg v Flovent Diskus
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3531
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-5.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.67
upper limit	6.32

Statistical analysis title	Change in AM PEF: Fp 100 - Flovent Diskus
Comparison groups	Fp MDPI 100 mcg v Flovent Diskus

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2724
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-6.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.35
upper limit	5.19

Statistical analysis title	Change in AM PEF: Fp 50 - Flovent Diskus
Comparison groups	Fp MDPI 50 mcg v Flovent Diskus
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3964
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-5.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.95
upper limit	6.72

Statistical analysis title	Change in AM PEF: Placebo - Flovent Diskus
Comparison groups	Placebo MDPI v Flovent Diskus
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0296
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-13.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.57
upper limit	-1.33

Other pre-specified: Change From Baseline In Weekly Average Of Daily Trough

(Predose And Pre-Rescue Bronchodilator) Evening Peak Expiratory Flow (PEF) Over The 12-Week Treatment Period (Including the Flovent Diskus treatment arm)

End point title	Change From Baseline In Weekly Average Of Daily Trough (Predose And Pre-Rescue Bronchodilator) Evening Peak Expiratory Flow (PEF) Over The 12-Week Treatment Period (Including the Flovent Diskus treatment arm)

End point description:

Peak expiratory flow was determined in the AM and in the PM, before administration of study or rescue medications using a handheld electronic peak flow meter. The highest value of triplicate measurements obtained was recorded by the subject's diary device.
PM PEF baseline was defined as the average of recorded (nonmissing) PM PEF assessments over the 7 days directly preceding first study drug intake.

The p-values for the treatment comparisons to Flovent Diskus are from an MMRM model that included data for all treatments: change from baseline = baseline PEF + sex + age + treatment + visit + treatment*visit with an unstructured covariance matrix assumed.

End point type	Other pre-specified

End point timeframe:

Baseline (Days -6 to Day 1 pre-dose), Weeks 1, 2, 3, 4, 6, 8, 10 and 12

End point values	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg	Fp MDPI 400 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	103[103]	99[104]	96[105]	102[106]
Units: liters/minute				
least squares mean (standard error)	4.22 (± 4.245)	6.52 (± 4.275)	7.89 (± 4.397)	11.72 (± 4.271)

Notes:

[103] - Full analysis set

[104] - Full analysis set

[105] - Full analysis set

[106] - Full analysis set

End point values	Placebo MDPI	Flovent Diskus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96[107]	99[108]		
Units: liters/minute				
least squares mean (standard error)	3.35 (± 4.518)	12.4 (± 4.309)		

Notes:

[107] - Full analysis set

[108] - Full analysis set

Statistical analyses

Statistical analysis title	Change in PM PEF: Fp 400 - Flovent Diskus
Comparison groups	Fp MDPI 400 mcg v Flovent Diskus
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9101
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.59
upper limit	11.22

Statistical analysis title	Change in PM PEF: Fp 200 - Flovent Diskus
Comparison groups	Fp MDPI 200 mcg v Flovent Diskus
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4634
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-4.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.6
upper limit	7.57

Statistical analysis title	Change in PM PEF: Fp 100 - Flovent Diskus
Comparison groups	Fp MDPI 100 mcg v Flovent Diskus
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3333
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-5.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	6.05

Statistical analysis title	Change in PM PEF: Fp 50 - Flovent Diskus
Comparison groups	Fp MDPI 50 mcg v Flovent Diskus

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1763
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-8.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.06
upper limit	3.69

Statistical analysis title	Change in PM PEF: Placebo - Flovent Diskus
Comparison groups	Placebo MDPI v Flovent Diskus
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1469
Method	Regression, Linear
Parameter estimate	LSM difference
Point estimate	-9.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.3
upper limit	3.19

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 16

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Fp MDPI 50 mcg

Reporting group description:

Fluticasone propionate (Fp) 50 mcg per dose twice a day (for a total daily dose of 100 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 100 mcg

Reporting group description:

Fluticasone propionate (Fp) 100 mcg per dose twice a day (for a total daily dose of 200 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).
During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 200 mcg

Reporting group description:

Fluticasone propionate (Fp) 200 mcg per dose twice a day (for a total daily dose of 400 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Fp MDPI 400 mcg

Reporting group description:

Fluticasone propionate (Fp) 400 mcg per dose twice a day (for a total daily dose of 800 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Placebo MDPI

Reporting group description:

Placebo twice a day using a multidose dry powder inhaler (MDPI) for 12 weeks in a double-blind manner (investigator and subject blinded).

During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on an as needed basis for the relief of asthma symptoms.

Reporting group title	Flovent Diskus

Reporting group description:

Fluticasone propionate (Fp) 250 mcg per dose twice a day (for a total daily dose of 500 mcg) using a multidose dry powder inhaler (MDPI) for 12 weeks in an open-label manner.
During the run-in and the treatment periods, all subjects replaced their current rescue medication with albuterol/salbutamol hydrofluoroalkane (HFA) metered dose inhaler (MDI) (90 mcg/actuation) for use on

Serious adverse events	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	1 / 106 (0.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Kidney infection			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Fp MDPI 400 mcg	Placebo MDPI	Flovent Diskus
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 106 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Prostate cancer			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 107 (0.00%)	1 / 106 (0.94%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Kidney infection			
subjects affected / exposed	0 / 107 (0.00%)	0 / 106 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Fp MDPI 50 mcg	Fp MDPI 100 mcg	Fp MDPI 200 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 107 (4.67%)	4 / 107 (3.74%)	5 / 106 (4.72%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 107 (4.67%)	4 / 107 (3.74%)	5 / 106 (4.72%)
occurrences (all)	5	10	6

Non-serious adverse events	Fp MDPI 400 mcg	Placebo MDPI	Flovent Diskus
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 107 (6.54%)	6 / 106 (5.66%)	4 / 106 (3.77%)
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 9	6 / 106 (5.66%) 9	4 / 106 (3.77%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2011	Amendment 1 to the protocol was issued before any subjects were enrolled into the study (first patient in [FPI] = 30 April 2012). Amendment 1 was made in 2 parts (leading to protocol versions 2.0 and 3.0) and involved changing study design to double-dummy (this protocol amendment was not implemented) and correcting a format error in Section 7.0 of the protocol.
15 August 2011	Amendment 2 to the protocol was issued before any subjects were enrolled into the study. In this amendment, study design reverted to the design presented in the original protocol and minor formatting and administrative changes were made.
10 February 2012	Amendment 3 to the protocol was issued before any subjects were enrolled into the study. In this amendment, the study visit schedule was revised to provide additional safety monitoring of subjects, and inclusion/exclusion criteria were modified to better define the study population. A total of 3 subjects were randomized to the study under this version of the protocol.
30 April 2012	Amendment 4 modified inclusion/exclusion criteria to clarify the study population. A total of 23 subjects were randomized to the study under this version of the protocol.
30 July 2012	Amendment 5 to the protocol modified inclusion criteria to clarify the study population. Changes to the protocol were considered to have no negative impact on the safety of subjects already enrolled into the study. A total of 84 subjects were randomized to the study under this version of the protocol.
20 December 2012	Amendment 6 modified inclusion criteria to allow retesting and rescreening and the dosage for permitted ICS was updated. Changes to the protocol were considered to have no negative impact on the safety of subjects already enrolled into the study. A total of 530 subjects were randomized to the study under this version of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported