Clinical trial results:
A 12-Week, Double-Blinded, 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

Summary

EudraCT number	2014-000923-25
Trial protocol	CZ DE HU PL
Global end of trial date	26 September 2015

Results information

Result version number	v1 (current)
This version publication date	18 May 2016
First version publication date	18 May 2016

Trial information

Trial identification

Sponsor protocol code	FSS-AS-30017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02141854
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., 1 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 1 215-591-3000, ustevatrials@tevapharm.com

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	16 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study 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.

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 good clinical practice in the conduct of clinical trials on medicinal products for human use). Information regarding any investigational centers participating in this study that could not comply with these standards was documented.
Written and/or oral information about the study was provided to all patients (or, in the case of minor patients [age 12 to 17 years or per local regulations], to patients and their parents/legally authorized representatives) in a language understandable by the patients (to the extent practical for minor patients) and/or representatives. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained before any study procedures or assessments were done. It was explained that patients were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each patient’s willingness to participate in the study was documented in writing in an informed consent form (ICF) that was signed by the patient (or legally acceptable representative) with the date of that signature indicated. Each investigator kept the original ICFs, and copies were given to the patients. Analogous procedures applied to assent forms.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2014
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	Canada: 3
Country: Number of subjects enrolled	United States: 540
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Ukraine: 36
Country: Number of subjects enrolled	Poland: 137
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Hungary: 98

Worldwide total number of subjects	882
EEA total number of subjects	240

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)	64
Adults (18-64 years)	722
From 65 to 84 years	96
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1661 patients with persistent asthma were screened and 882 patients enrolled. 154 patients were not randomized, most commonly (76 patients) because of not meeting randomization criteria.

Period 1

Period 1 title	Run-In Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

All patients replace their current inhaled corticosteroid and instead take 1 inhalation twice a day from a single-blinded fluticasone propionate 50 mcg multidose dry powder inhaler device.

Arms

Arm title	Fluticasone Propionate 50 mcg BID

Arm description:

During the 14-21 day run-in period, patients discontinued their current inhaled corticosteroid and instead took a single-blinded fluticasone propionate (Fp) multidose dry powder inhaler (MDPI) 50 mcg 1 inhalation twice a day for a total daily dose of 100 mcg. Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI), a short acting beta2 adrenergic agonist (SABA) inhaler, was provided to replace the patient's current rescue medication.

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

Dosage and administration details:

Fluticasone propionate multidose dry powder inhaler (Fp MDPI) 50 mcg in the morning and evening for a total daily dose of 100 mcg.

Investigational medicinal product name	Albuterol/Salbutamol
Investigational medicinal product code	
Other name	ProAir
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Albuterol/salbutamol hydrofluoroalkane (specifically, HFA 134a) metered dose inhaler (MDI), for use on an as-needed basis for the immediate relief of asthma symptoms.

Number of subjects in period 1	Fluticasone Propionate 50 mcg BID
Started	882
Completed	728
Not completed	154
Exclusion criteria met	14
Consent withdrawn by subject	9
Adverse event, non-fatal	10
Not specified	14
Randomization criteria not met	76
Lost to follow-up	6
Inclusion criteria not met	25

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Patients were randomly assigned to one of 5 treatments; a permanent unique randomization number and treatment kit number was generated using interactive response technology (IRT). Patients and investigators remained blinded to treatment assignment during the study.
The sponsor's clinical personnel involved in the study were blinded until the database was locked for analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo MDPI

Arm description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of placebo for 12 weeks.

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:

The placebo multidose dry powder inhaler was identical to the devices used to deliver active drug, and indistinguishable from the active treatments. Patients took one inhalation twice a day (approximately 12 hours apart). Patients were instructed to rinse their mouth and expectorate (not swallow) after study drug administration.

Arm title	Fp MDPI 100 mcg

Arm description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 200 mcg for 12 weeks.

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

Dosage and administration details:

Fluticasone propionate multidose dry powder inhaler (Fp MDPI) 100 mcg in the morning and evening for a total daily dose of 200 mcg. Patients were instructed to rinse their mouth and expectorate (not swallow) after study drug administration.

Arm title	Fp MDPI 200 mcg

Arm description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 400 mcg for 12 weeks.

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

Dosage and administration details:

Fluticasone propionate multidose dry powder inhaler (Fp MDPI) 200 mcg in the morning and evening for a total daily dose of 400 mcg. Patients were instructed to rinse their mouth and expectorate (not swallow) after study drug administration.

Arm title	FS MDPI 100 / 12.5 mcg

Arm description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 100 mcg (for a total daily dose of 200 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks.

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

Dosage and administration details:

Fluticasone propionate (combined with salmeterol) multidose dry powder inhaler 100 mcg in the morning and evening for a total daily dose of 200 mcg. Patients were instructed to rinse their mouth and expectorate (not swallow) after study drug administration.

Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol (combined with fluticasone propionate) multidose dry powder inhaler 12.5 mcg in the morning and evening for a total daily dose of 25 mcg. Patients were instructed to rinse their mouth and expectorate (not swallow) after study drug administration.

Arm title	FS MDPI 200 / 12.5 mcg

Arm description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 200 mcg (for a total daily dose of 400 mcg) and salmeterol 12.5 mcg (for a total daily dose

of 25 mcg) for 12 weeks.

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

Dosage and administration details:

Fluticasone propionate (combined with salmeterol) multidose dry powder inhaler 200 mcg in the morning and evening for a total daily dose of 400 mcg. Patients were instructed to rinse their mouth and expectorate (not swallow) after study drug administration.

Investigational medicinal product name	Salmeterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol (combined with fluticasone propionate) multidose dry powder inhaler 12.5 mcg in the morning and evening for a total daily dose of 25 mcg. Patients were instructed to rinse their mouth and expectorate (not swallow) after study drug administration.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the Run-In Period in which all patients were given the same medications and qualifying tests. Patients who successfully met study criteria were randomized and treated in the Treatment Period. Hence baseline information is offered for those patients who entered the Treatment Period.

Number of subjects in period 2[2]	Placebo MDPI	Fp MDPI 100 mcg	Fp MDPI 200 mcg
Started	145	146	146
Intent to treat population	145	146	146
Safety population	144	145	146
Full analysis set	143	145	146
Completed	107	136	135
Not completed	38	10	11
Consent withdrawn by subject	7	4	3
Disease progression	18	-	3
Adverse event, non-fatal	2	2	-
Not specified	2	1	-
Pregnancy	-	-	-
Non-compliance	-	-	1
Lost to follow-up	1	-	1
Protocol deviation	1	2	2
Lack of efficacy	7	1	1

Number of subjects in period 2[2]	FS MDPI 100 / 12.5 mcg	FS MDPI 200 / 12.5 mcg
Started	145	146
Intent to treat population	145	146

Safety population	143	145
Full analysis set	141	145
Completed	136	136
Not completed	9	10
Consent withdrawn by subject	3	2
Disease progression	1	2
Adverse event, non-fatal	2	2
Not specified	2	1
Pregnancy	-	1
Non-compliance	-	-
Lost to follow-up	1	1
Protocol deviation	-	1
Lack of efficacy	-	-

Notes:

[2] - 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: The number of subjects enrolled matches the number of subjects in the Run-In Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo MDPI
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of placebo for 12 weeks.	
Reporting group title	Fp MDPI 100 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 200 mcg for 12 weeks.	
Reporting group title	Fp MDPI 200 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 400 mcg for 12 weeks.	
Reporting group title	FS MDPI 100 / 12.5 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 100 mcg (for a total daily dose of 200 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks.	
Reporting group title	FS MDPI 200 / 12.5 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 200 mcg (for a total daily dose of 400 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks.	

Reporting group values	Placebo MDPI	Fp MDPI 100 mcg	Fp MDPI 200 mcg
Number of subjects	145	146	146
Age categorical			
ITT population			
Units: Subjects			
Adolescents (12-17 years)	6	9	10
Adults (18-64 years)	125	124	119
From 65-84 years	14	13	17
Age continuous			
ITT population			
Units: years			
arithmetic mean	44.5	45.7	44.4
standard deviation	± 16.05	± 15.64	± 16.36
Gender categorical			
ITT population			
Units: Subjects			
Female	91	94	88
Male	54	52	58
Race			
ITT population			
Units: Subjects			
White	124	111	116
Black or African American	18	31	23
Asian	2	0	2
American Indian or Alaska Native	0	0	2

Native Hawaiian or other Pacific Islander	0	0	0
Other	1	4	3
Ethnicity			
ITT population			
Units: Subjects			
Not Hispanic or Latino	136	134	136
Hispanic or Latino	8	11	10
Unknown	1	1	0
History of Smoking			
ITT population			
Units: Subjects			
Prior Smoker	23	28	21
No tobacco use	122	118	125
Previous Asthma Therapy			
ITT population			
Units: Subjects			
Inhaled corticosteroid	68	58	63
Inhaled corticosteroid/long-acting beta2-agonist	77	88	83
Body Mass Index			
ITT population			
Units: kg/m^2			
arithmetic mean	29.3	29.9	29.9
standard deviation	± 7.41	± 7.62	± 7.27
Forced Expiratory Volune in 1 second (FEV1)			
n=144, 145, 146, 142, 145			
Units: liters			
arithmetic mean	2.141	2.069	2.075
standard deviation	± 0.6849	± 0.6017	± 0.5696

Reporting group values	FS MDPI 100 / 12.5 mcg	FS MDPI 200 / 12.5 mcg	Total
Number of subjects	145	146	728
Age categorical			
ITT population			
Units: Subjects			
Adolescents (12-17 years)	8	12	45
Adults (18-64 years)	125	115	608
From 65-84 years	12	19	75
Age continuous			
ITT population			
Units: years			
arithmetic mean	44.3	44.7	
standard deviation	± 14.88	± 16.93	-
Gender categorical			
ITT population			
Units: Subjects			
Female	79	87	439
Male	66	59	289

Race			
ITT population			
Units: Subjects			
White	112	125	588
Black or African American	28	20	120
Asian	0	0	4
American Indian or Alaska Native	0	0	2
Native Hawaiian or other Pacific Islander	0	0	0
Other	5	1	14
Ethnicity			
ITT population			
Units: Subjects			
Not Hispanic or Latino	135	136	677
Hispanic or Latino	10	10	49
Unknown	0	0	2
History of Smoking			
ITT population			
Units: Subjects			
Prior Smoker	28	20	120
No tobacco use	117	126	608
Previous Asthma Therapy			
ITT population			
Units: Subjects			
Inhaled corticosteroid	67	73	329
Inhaled corticosteroid/long-acting beta2-agonist	78	73	399
Body Mass Index			
ITT population			
Units: kg/m^2			
arithmetic mean	30.2	29.4	
standard deviation	± 7.6	± 7.35	-
Forced Expiratory Volune in 1 second (FEV1)			
n=144, 145, 146, 142, 145			
Units: liters			
arithmetic mean	2.157	2.083	
standard deviation	± 0.6402	± 0.6532	-

End points

End points reporting groups

Reporting group title	Fluticasone Propionate 50 mcg BID

Reporting group description:

During the 14-21 day run-in period, patients discontinued their current inhaled corticosteroid and instead took a single-blinded fluticasone propionate (Fp) multidose dry powder inhaler (MDPI) 50 mcg 1 inhalation twice a day for a total daily dose of 100 mcg. Albuterol/salbutamol hydrofluoroalkane (HFA) metered-dose inhaler (MDI), a short acting beta2 adrenergic agonist (SABA) inhaler, was provided to replace the patient's current rescue medication.

Reporting group title	Placebo MDPI

Reporting group description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of placebo for 12 weeks.

Reporting group title	Fp MDPI 100 mcg

Reporting group description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 200 mcg for 12 weeks.

Reporting group title	Fp MDPI 200 mcg

Reporting group description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 400 mcg for 12 weeks.

Reporting group title	FS MDPI 100 / 12.5 mcg

Reporting group description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 100 mcg (for a total daily dose of 200 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks.

Reporting group title	FS MDPI 200 / 12.5 mcg

Reporting group description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 200 mcg (for a total daily dose of 400 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks.

Subject analysis set title	FS MDPI 200 / 12.5 mcg
Subject analysis set type	Full analysis

Subject analysis set description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 200 mcg (for a total daily dose of 400 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks. The full analysis set included intent-to-treat patients with >=1 dose of study drug and >=1 postbaseline trough FEV1.

Subject analysis set title	FS MDPI 100 / 12.5 mcg
Subject analysis set type	Full analysis

Subject analysis set description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 100 mcg (for a total daily dose of 200 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks. The full analysis set included intent-to-treat patients with >=1 dose of study drug and >=1 postbaseline trough FEV1.

Subject analysis set title	Fp MDPI 200 mcg
Subject analysis set type	Full analysis

Subject analysis set description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 400 mcg for 12 weeks. The full analysis set included intent-to-treat patients with >=1 dose of study drug and >=1 postbaseline trough FEV1.

Subject analysis set title	Fp MDPI 100 mcg
Subject analysis set type	Full analysis

Subject analysis set description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone

propionate for a total daily dose of 200 mcg for 12 weeks. The full analysis set included intent-to-treat patients with >=1 dose of study drug and >=1 postbaseline trough FEV1.

Subject analysis set title	Placebo MDPI
Subject analysis set type	Full analysis

Subject analysis set description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of placebo for 12 weeks. The full analysis set included intent-to-treat patients with >=1 dose of study drug and >=1 postbaseline trough FEV1.

Subject analysis set title	Serial Spirometry Subset:FS MDPI 200 / 12.5 mcg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of patients who performed postdose serial spirometry at the baseline visit and week 12, and were randomized to the fluticasone propionate 200 mcg and salmeterol 12.5 mcg/dose BID treatment group.

Subject analysis set title	Serial Spirometry Subset:FS MDPI 100 / 12.5 mcg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of patients who performed postdose serial spirometry at the baseline visit and week 12, and were randomized to the fluticasone propionate 100 mcg and salmeterol 12.5 mcg/dose BID treatment group.

Subject analysis set title	Serial Spirometry Subset: Fp MDPI 200 mcg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of patients who performed postdose serial spirometry at the baseline visit and week 12, and were randomized to the fluticasone propionate 200 mcg/dose BID treatment group.

Subject analysis set title	Serial Spirometry Subset: Fp MDPI 100 mcg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of patients who performed postdose serial spirometry at the baseline visit and week 12, and were randomized to the fluticasone propionate 100 mcg/dose BID treatment group.

Subject analysis set title	Serial Spirometry Subset: Placebo MDPI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subset of patients who performed postdose serial spirometry at the baseline visit and week 12, and were randomized to the placebo treatment group.

Primary: Standardized Baseline-Adjusted Forced Expiratory Volume in 1 Second (FEV1) Area Under the Effect Curve from Time Zero to 12 Hours PostDose (FEV1 AUEC0-12) at Week 12

End point title	Standardized Baseline-Adjusted Forced Expiratory Volume in 1 Second (FEV1) Area Under the Effect Curve from Time Zero to 12 Hours PostDose (FEV1 AUEC0-12) at Week 12

End point description:

A subset of patients performed postdose serial spirometry. Data from these assessments were used to analyze the primary endpoint of baseline-adjusted FEV1 AUEC0-12h at week 12 using the trapezoidal rule based on actual time of measurement. It was standardized by dividing it by the number of hours between the start time of dose administration and the end time of the last nonmissing FEV1 measurement. The baseline FEV1 was the average of the 2 predose FEV1 measurements (30 and 10 minutes predose). If 1 of these was missing, the nonmissing value was used; if both were missing, baseline was treated as missing. Baseline-adjusted FEV1 was calculated as postdose FEV1 after subtracting the baseline FEV1 value.

End point type	Primary

End point timeframe:

Day 1 (predose, baseline), Week 12 and was performed at the following times relative to the administration of study drug (±5 minutes): 15 and 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours.

End point values	Serial Spirometry Subset:FS MDPI 200 / 12.5 mcg	Serial Spirometry Subset:FS MDPI 100 / 12.5 mcg	Serial Spirometry Subset: Fp MDPI 200 mcg	Serial Spirometry Subset: Fp MDPI 100 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	58	61	64
Units: liters				
least squares mean (standard error)	0.446 (± 0.0463)	0.442 (± 0.0496)	0.267 (± 0.0466)	0.26 (± 0.0463)

End point values	Serial Spirometry Subset: Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: liters				
least squares mean (standard error)	0.121 (± 0.0472)			

Statistical analyses

Statistical analysis title	AUEC0-12: FS 200/12.5 vs Fp 200 mcg

Statistical analysis description:

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 analyses. Analyses appear in the defined sequence. This is the first in the sequence.

Comparison groups	Serial Spirometry Subset:FS MDPI 200 / 12.5 mcg v Serial Spirometry Subset: Fp MDPI 200 mcg
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [1]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.179
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.285

Notes:

[1] - Fixed effects of treatment, sex, (pooled) center, previous therapy (ICS or ICS/LABA), and covariates of age and baseline FEV1.

Statistical analysis title	AUEC0-12: FS 100/12.5 vs Fp 100 mcg

Statistical analysis description:

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 analyses. Analyses appear in the defined sequence. This is the second in the sequence.

Comparison groups	Serial Spirometry Subset:FS MDPI 100 / 12.5 mcg v Serial Spirometry Subset: Fp MDPI 100 mcg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [2]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.182
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.291

Notes:

[2] - Fixed effects of treatment, sex, (pooled) center, previous therapy (ICS or ICS/LABA), and covariates of age and baseline FEV1.

Statistical analysis title	AUEC0-12: FS 200/12.5 mcg vs Placebo

Statistical analysis description:

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 analyses. Analyses appear in the defined sequence. This is the third in the sequence.

Comparison groups	Serial Spirometry Subset:FS MDPI 200 / 12.5 mcg v Serial Spirometry Subset: Placebo MDPI
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [3]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.326
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.221
upper limit	0.431

Notes:

[3] - Fixed effects of treatment, sex, (pooled) center, previous therapy (ICS or ICS/LABA), and covariates of age and baseline FEV1.

Statistical analysis title	AUEC0-12: FS 100/12.5 mcg vs Placebo

Statistical analysis description:

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 analyses. Analyses appear in the defined sequence. This is the fourth in the sequence.

Comparison groups	Serial Spirometry Subset:FS MDPI 100 / 12.5 mcg v Serial Spirometry Subset: Placebo MDPI

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [4]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.322
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.212
upper limit	0.432

Notes:

[4] - Fixed effects of treatment, sex, (pooled) center, previous therapy (ICS or ICS/LABA), and covariates of age and baseline FEV1.

Primary: Change from Baseline in Morning Trough Forced Expiratory Volume in 1 Second (FEV1) at Week 12

End point title	Change from Baseline in Morning Trough Forced Expiratory Volume in 1 Second (FEV1) at Week 12

End point description:

Trough FEV1 is a morning spirometry taken predose and pre-rescue bronchodilator. If the patient inadvertently administered asthma medication/study drug at home on the AM of the visit, or if the patient took rescue medication within 6 hours of testing, the visit was rescheduled.
The baseline for predose FEV1 was defined as the average of the 30-minute and 10-minute predose measurements obtained at the randomization visit (Day 1).

End point type	Primary

End point timeframe:

Day 1 (predose, baseline), Week 12

End point values	FS MDPI 200 / 12.5 mcg	FS MDPI 100 / 12.5 mcg	Fp MDPI 200 mcg	Fp MDPI 100 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	143	140	145	144
Units: liters				
least squares mean (standard error)	0.272 (± 0.0307)	0.271 (± 0.0311)	0.179 (± 0.0308)	0.119 (± 0.0311)

End point values	Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	143			
Units: liters				
least squares mean (standard error)	-0.004 (± 0.0312)			

Statistical analyses

Statistical analysis title	FEV1: FS 200/12.5 mcg vs Placebo

Statistical analysis description:

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 analyses. Analyses appear in the defined sequence. This is the fifth in the sequence.

Comparison groups	FS MDPI 200 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [5]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.276
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.191
upper limit	0.361

Notes:

[5] - Effects due to baseline trough AM FEV1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment.

Statistical analysis title	FEV1: FS 100/12.5 mcg vs Placebo

Statistical analysis description:

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 analyses. Analyses appear in the defined sequence. This is the sixth in the sequence.

Comparison groups	FS MDPI 100 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [6]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.274
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.189
upper limit	0.36

Notes:

[6] - Effects due to baseline trough AM FEV1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment.

Statistical analysis title	FEV1: Fp 200 mcg vs Placebo

Statistical analysis description:

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 analyses. Analyses appear in the defined sequence. This is the seventh in the sequence.

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI

Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [7]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.098
upper limit	0.268

Notes:

[7] - Effects due to baseline trough AM FEV1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment.

Statistical analysis title	FEV1: Fp 100 mcg vs Placebo

Statistical analysis description:

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 analyses. Analyses appear in the defined sequence. This is the eighth in the sequence.

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047 [8]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.208

Notes:

[8] - Effects due to baseline trough AM FEV1, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment.

Secondary: Change from Baseline in the Weekly Average of the Daily Morning Trough Peak Expiratory Flow (PEF) Over the 12 Week Treatment

End point title	Change from Baseline in the Weekly Average of the Daily Morning Trough Peak Expiratory Flow (PEF) Over the 12 Week Treatment

End point description:

Morning PEF tests were performed before administration of study drug or rescue medications (data were excluded if the time of PEF measurement was more than 5 minutes after the dose time). The patient recorded the highest value of 3 measurements obtained in the patient diary.

The baseline PEF was the average value of recorded (nonmissing) morning assessments over the 7 days prior to randomization on Day 1. For efficacy analyses of weekly average morning PEF measurements, values were the averages based on available data for that week.

End point type	Secondary

End point timeframe:

Days -6 to Day 1 (predose, baseline), Day 1 (postdose) daily until Week 12

End point values	FS MDPI 200 / 12.5 mcg	FS MDPI 100 / 12.5 mcg	Fp MDPI 200 mcg	Fp MDPI 100 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145	141	146	145
Units: liters/minute				
least squares mean (standard error)	20.235 (± 2.3845)	18.61 (± 2.4137)	7.464 (± 2.3887)	5.731 (± 2.4102)

End point values	Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	142			
Units: liters/minute				
least squares mean (standard error)	-10.987 (± 2.4784)			

Statistical analyses

Statistical analysis title	AM PEF: Fp 200 mcg vs Placebo

Statistical analysis description:

The analysis of change from baseline in weekly average of daily (AM predose and pre rescue bronchodilator) PEF over the 12-week treatment period was performed using an mixed model for repeated measures (MMRM) with an unstructured covariance matrix and with effects due to baseline weekly average of daily AM PEF, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [9]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	18.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.751
upper limit	25.15

Notes:

[9] - Significance level of 0.05.

Statistical analysis title	AM PEF: Fp 100 mcg vs Placebo

Statistical analysis description:

The analysis of change from baseline in weekly average of daily (AM predose and pre rescue bronchodilator) PEF over the 12-week treatment period was performed using an mixed model for repeated measures (MMRM) with an unstructured covariance matrix and with effects due to baseline

weekly average of daily AM PEF, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [10]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	16.718
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.988
upper limit	23.449

Notes:

[10] - Significance level of 0.05.

Statistical analysis title	AM PEF: FS 200/12.5 mcg vs Placebo

Statistical analysis description:

The analysis of change from baseline in weekly average of daily (AM predose and pre rescue bronchodilator) PEF over the 12-week treatment period was performed using an mixed model for repeated measures (MMRM) with an unstructured covariance matrix and with effects due to baseline weekly average of daily AM PEF, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 200 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [11]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	31.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.513
upper limit	37.93

Notes:

[11] - Significance level of 0.05.

Statistical analysis title	AM PEF: FS 100/12.5 mcg vs Placebo

Statistical analysis description:

The analysis of change from baseline in weekly average of daily (AM predose and pre rescue bronchodilator) PEF over the 12-week treatment period was performed using an mixed model for repeated measures (MMRM) with an unstructured covariance matrix and with effects due to baseline weekly average of daily AM PEF, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Placebo MDPI

Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [12]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	29.597
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.839
upper limit	36.354

Notes:

[12] - Significance level of 0.05.

Statistical analysis title	AM PEF: FS 200/12.5 mcg vs FP 200 mcg

Statistical analysis description:

The analysis of change from baseline in weekly average of daily (AM predose and pre rescue bronchodilator) PEF over the 12-week treatment period was performed using an mixed model for repeated measures (MMRM) with an unstructured covariance matrix and with effects due to baseline weekly average of daily AM PEF, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 200 / 12.5 mcg v Fp MDPI 200 mcg
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [13]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	12.771
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.179
upper limit	19.363

Notes:

[13] - Significance level of 0.05.

Statistical analysis title	AM PEF: FS 100/12.5 mcg vs FP 100 mcg

Statistical analysis description:

The analysis of change from baseline in weekly average of daily (AM predose and pre rescue bronchodilator) PEF over the 12-week treatment period was performed using an mixed model for repeated measures (MMRM) with an unstructured covariance matrix and with effects due to baseline weekly average of daily AM PEF, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [14]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	12.879

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.216
upper limit	19.541

Notes:

[14] - Significance level of 0.05.

Statistical analysis title	AM PEF: FS 100/12.5 mcg vs FP 200 mcg

Statistical analysis description:

The analysis of change from baseline in weekly average of daily (AM predose and pre rescue bronchodilator) PEF over the 12-week treatment period was performed using an mixed model for repeated measures (MMRM) with an unstructured covariance matrix and with effects due to baseline weekly average of daily AM PEF, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 200 mcg
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [15]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	11.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.511
upper limit	17.782

Notes:

[15] - Significance level of 0.05.

Secondary: Change from Baseline in the Weekly Average of the Total Daily Asthma Symptom Score Over the 12-Week Treatment Period

End point title	Change from Baseline in the Weekly Average of the Total Daily Asthma Symptom Score Over the 12-Week Treatment Period

End point description:

The total daily asthma symptom score is the average of the daytime and nighttime scores as recorded in the patient diary.
Daytime Symptom Score:
0=No symptoms
1=Symptoms for 1 short period
2=Symptoms for 2+ short periods
3=Symptoms for most of the day - did not affect normal daily activities
4=Symptoms for most of the day - did affect normal daily activities
5=Symptoms so severe that I could not go to work or perform normal daily activities
Nighttime Symptom Score (determined in the AM):
0=No symptoms
1=Symptoms causing me to wake once (or wake early)
2=Symptoms causing me to wake twice or more (including waking early)
3=Symptoms causing me to be awake for most of the night
4=Symptoms so severe that I did not sleep
Baseline was the average of recorded scores over the 7 days before randomization. The change from baseline in the weekly average over weeks 1 to 12 was analyzed using an mixed model for repeated measures (MMRM).

End point type	Secondary

End point timeframe:

Days -6 to Day 1 (predose, baseline), to Week 12

End point values	FS MDPI 200 / 12.5 mcg	FS MDPI 100 / 12.5 mcg	Fp MDPI 200 mcg	Fp MDPI 100 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145	141	146	145
Units: units on a scale				
least squares mean (standard error)	-0.391 (± 0.0328)	-0.364 (± 0.0332)	-0.242 (± 0.0329)	-0.282 (± 0.0333)

End point values	Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	142			
Units: units on a scale				
least squares mean (standard error)	-0.087 (± 0.0342)			

Statistical analyses

Statistical analysis title	Asthma Symptoms: Fp 200 mcg vs Placebo

Statistical analysis description:

The change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 to 12 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [16]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.248
upper limit	-0.063

Notes:

[16] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: Fp 100 mcg vs Placebo

Statistical analysis description:

The change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 to 12 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [17]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.288
upper limit	-0.102

Notes:

[17] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 200/12.5 mcg vs Placebo

Statistical analysis description:

The change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 to 12 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 200 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [18]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.304
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.397
upper limit	-0.212

Notes:

[18] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 100/12.5 mcg vs Placebo

Statistical analysis description:

The change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 to 12 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [19]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.277

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.184

Notes:

[19] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 200/12.5 mcg vs Fp 200 mcg

Statistical analysis description:

The change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 to 12 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 200 / 12.5 mcg v Fp MDPI 200 mcg
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 [20]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.149
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.239
upper limit	-0.058

Notes:

[20] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 100/12.5 mcg vs Fp 100 mcg

Statistical analysis description:

The change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 to 12 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0818 [21]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.174
upper limit	-0.01

Notes:

[21] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 100/12.5 mcg vs Fp 200 mcg

Statistical analysis description:

The change from baseline in the weekly average of the total daily asthma symptom scores over weeks 1 to 12 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 200 mcg
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0094 [22]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.121
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.213
upper limit	-0.03

Notes:

[22] - Significance level of 0.05.

Secondary: Change from Baseline in the Weekly Average of the Total Daily (24-hour) Use of Albuterol/Salbutamol Inhalation Aerosol Over the 12-Week Treatment Period

End point title	Change from Baseline in the Weekly Average of the Total Daily (24-hour) Use of Albuterol/Salbutamol Inhalation Aerosol Over the 12-Week Treatment Period

End point description:

Patients recorded the number of inhalations of rescue medication (albuterol/salbutamol HFA MDI) each AM and PM in the diary. The average number of daily inhalations over the 7 days before the randomization visit was the baseline value. The weekly average was based on the available data for the 7 days before each analysis week.

The 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 was analyzed using a mixed model for repeated measures.

End point type	Secondary

End point timeframe:

Days -6 to Day 1 (predose, baseline), up to week 12

End point values	FS MDPI 200 / 12.5 mcg	FS MDPI 100 / 12.5 mcg	Fp MDPI 200 mcg	Fp MDPI 100 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145	141	146	145
Units: puffs				
least squares mean (standard error)	-0.898 (± 0.1069)	-0.821 (± 0.108)	-0.534 (± 0.107)	-0.439 (± 0.1081)

End point values	Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	143			
Units: puffs				
least squares mean (standard error)	0.168 (± 0.1102)			

Statistical analyses

Statistical analysis title	Rescue Meds: Fp 200 mcg vs Placebo

Statistical analysis description:

The 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 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline value, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [23]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.702
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.001
upper limit	-0.403

Notes:

[23] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: Fp 100 mcg vs Placebo

Statistical analysis description:

The 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 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline value, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [24]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.607
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.908
upper limit	-0.307

Notes:

[24] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: FS 200/12.5 mcg vs Placebo

Statistical analysis description:

The 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 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline value, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 200 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [25]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-1.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.365
upper limit	-0.766

Notes:

[25] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: FS 100/12.5 mcg vs Placebo

Statistical analysis description:

The 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 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline value, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [26]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.989
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.291
upper limit	-0.686

Notes:

[26] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: FS 200/12.5 mcg vs Fp 200 mcg

Statistical analysis description:

The 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 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline value, sex, age, (pooled) center,

previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 200 / 12.5 mcg v Fp MDPI 200 mcg
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [27]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.364
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.659
upper limit	-0.068

Notes:

[27] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: FS 100/12.5 mcg vs Fp 100 mcg

Statistical analysis description:

The 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 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline value, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124 [28]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.382
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.681
upper limit	-0.083

Notes:

[28] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: FS 100/12.5 mcg vs Fp 200 mcg

Statistical analysis description:

The 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 was analyzed using an MMRM with an unstructured covariance matrix and with effects due to baseline value, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 200 mcg

Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0588 [29]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.287
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.584
upper limit	-0.011

Notes:

[29] - Significance level of 0.05.

Secondary: Kaplan-Meier Estimate of Probability of Remaining in Study At Week 12

End point title	Kaplan-Meier Estimate of Probability of Remaining in 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, defined as the number of days elapsed from the date of randomization to the date of withdrawal due to worsening asthma. Patients who were lost to follow-up, who had not withdrawn due to worsening asthma by week 12, or 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:

up to Week 12 of the Treatment Period

End point values	FS MDPI 200 / 12.5 mcg	FS MDPI 100 / 12.5 mcg	Fp MDPI 200 mcg	Fp MDPI 100 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145	141	146	145
Units: probability				
number (confidence interval 95%)	0.9719 (0.927 to 0.989)	0.9929 (0.95 to 0.999)	0.9786 (0.935 to 0.993)	0.993 (0.951 to 0.999)

End point values	Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	143			
Units: probability				
number (confidence interval 95%)	0.8528 (0.781 to 0.903)			

Statistical analyses

Statistical analysis title	Probability 12 Weeks: Fp 200 mcg vs Placebo
Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [30]
Method	Logrank

Notes:

[30] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: Fp 100 mcg vs Placebo
Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	Logrank

Notes:

[31] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FS 200/12.5 mcg vs Placebo
Comparison groups	FS MDPI 200 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [32]
Method	Logrank

Notes:

[32] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FS 100/12.5 mcg vs Placebo
Comparison groups	FS MDPI 100 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [33]
Method	Logrank

Notes:

[33] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FS 200/12.5 mcg vs Fp 200 mc
Comparison groups	FS MDPI 200 / 12.5 mcg v Fp MDPI 200 mcg
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7203 [34]
Method	Logrank

Notes:

[34] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FS 100/12.5 mcg vs Fp100 mcg
Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.996 [35]
Method	Logrank

Notes:

[35] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FS 100/12.5 mcg vs Fp200 mcg
Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 200 mcg
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.325 [36]
Method	Logrank

Notes:

[36] - Significance level of 0.05.

Secondary: Change from Baseline in the Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) Score at Endpoint for Patients >=18 Years Old

End point title	Change from Baseline in the Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) Score at Endpoint for Patients >=18 Years Old

End point description:

The AQLQ(S) (September 2010 version; patients aged ≥18 years) was self administered by the patients at the investigational center at the randomization visit and at Week 12 or end of trial. The questionnaire is a tool to measure the impact of asthma on a patient's quality of life (physical, emotional, social, and occupational) with a recall period of 2 weeks. The AQLQ(S) was administered only to patients 18 years and older. The 32 individual questions in the AQLQ were equally weighted. The overall AQLQ score was the mean of the responses to each of the 32 questions, and ranged from 1 to 7. A score 7.0 indicated that the patient had no impairments due to asthma and a score of 1.0 indicated severe impairment. Positive change from baseline scores indicate improved quality of life.

End point type	Secondary

End point timeframe:

Day 1 (predose, baseline), end of trial (up to week 12)

End point values	FS MDPI 200 / 12.5 mcg	FS MDPI 100 / 12.5 mcg	Fp MDPI 200 mcg	Fp MDPI 100 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	131[37]	135[38]	132[39]	133[40]
Units: units on a scale				
least squares mean (standard error)	0.534 (± 0.0741)	0.592 (± 0.0725)	0.384 (± 0.0742)	0.34 (± 0.074)

Notes:

[37] - patients who contributed at least once to analysis and were >= 18 years old

[38] - patients who contributed at least once to analysis and were >= 18 years old

[39] - patients who contributed at least once to analysis and were >= 18 years old

[40] - patients who contributed at least once to analysis and were >= 18 years old

End point values	Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	129[41]			
Units: units on a scale				
least squares mean (standard error)	-0.089 (± 0.0747)			

Notes:

[41] - patients who contributed at least once to analysis and were >= 18 years old

Statistical analyses

Statistical analysis title	AQLQ(S): Fp 200 mcg vs Placebo

Statistical analysis description:

The change from baseline in AQLQ(S) score (patients ≥18 years of age) at endpoint (ie, last postbaseline observation) was analyzed using an ANCOVA model with effects due to baseline AQLQ(S) score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data via last observation carried forward (LOCF).

Comparison groups	Fp MDPI 200 mcg v Placebo MDPI
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [42]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.473
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.269
upper limit	0.677

Notes:

[42] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): Fp 100 mcg vs Placebo

Statistical analysis description:

The change from baseline in AQLQ(S) score (patients ≥18 years of age) at endpoint (ie, last postbaseline observation) was analyzed using an ANCOVA model with effects due to baseline AQLQ(S) score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data via last observation carried forward (LOCF).

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [43]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.428

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.224
upper limit	0.632

Notes:

[43] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): FS 200/12.5 mcg vs Placebo

Statistical analysis description:

The change from baseline in AQLQ(S) score (patients ≥18 years of age) at endpoint (ie, last postbaseline observation) was analyzed using an ANCOVA model with effects due to baseline AQLQ(S) score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data via last observation carried forward (LOCF).

Comparison groups	FS MDPI 200 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [44]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.623
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.418
upper limit	0.828

Notes:

[44] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): FS 100/12.5 mcg vs Placebo

Statistical analysis description:

The change from baseline in AQLQ(S) score (patients ≥18 years of age) at endpoint (ie, last postbaseline observation) was analyzed using an ANCOVA model with effects due to baseline AQLQ(S) score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data via last observation carried forward (LOCF).

Comparison groups	FS MDPI 100 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [45]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.681
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.478
upper limit	0.885

Notes:

[45] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): FS 200/12.5 mcg vs Fp 200 mcg

Statistical analysis description:

The change from baseline in AQLQ(S) score (patients ≥18 years of age) at endpoint (ie, last postbaseline observation) was analyzed using an ANCOVA model with effects due to baseline AQLQ(S) score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data via last observation carried forward (LOCF).

Comparison groups	FS MDPI 200 / 12.5 mcg v Fp MDPI 200 mcg
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.149 [46]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.054
upper limit	0.354

Notes:

[46] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): FS 100/12.5 mcg vs Fp 100 mcg

Statistical analysis description:

The change from baseline in AQLQ(S) score (patients ≥18 years of age) at endpoint (ie, last postbaseline observation) was analyzed using an ANCOVA model with effects due to baseline AQLQ(S) score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data via last observation carried forward (LOCF).

Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0143 [47]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.253
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.455

Notes:

[47] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): FS 100/12.5 mcg vs Fp 200 mcg

Statistical analysis description:

The change from baseline in AQLQ(S) score (patients ≥18 years of age) at endpoint (ie, last postbaseline observation) was analyzed using an ANCOVA model with effects due to baseline AQLQ(S) score, sex, age, (pooled) center, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data via last observation carried forward (LOCF).

Comparison groups	FS MDPI 100 / 12.5 mcg v Fp MDPI 200 mcg

Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0435 [48]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.411

Notes:

[48] - Significance level of 0.05.

Secondary: Kaplan-Meier Estimates for Time to 15% and 12% Improvement from Baseline in FEV1 Postdose on Day 1

End point title	Kaplan-Meier Estimates for Time to 15% and 12% Improvement from Baseline in FEV1 Postdose on Day 1

End point description:

The baseline forced expiratory volume in 1 second (FEV1) was the average of the 2 predose FEV1 measurements (30 and 10 minutes predose) on Day 1. If one of these was missing, the other measurement was used as baseline value. If both were missing, the baseline trough FEV1 was treated as missing.
Time to target improvement (15% or 12%) was defined as the time elapsed from the time of first dose to the first time the target improvement in FEV1 was achieved. If an exact target increase was not achieved at a measured timepoint, then the time was estimated by linear interpolation between the timepoint when target was reached and the timepoint immediately before. Patients who did not achieve the target improvement were censored at the time of last serial spirometry assessment.
Values of 9999 indicate the values could not be estimated which happened when the estimated probability of not achieving target is more than 50%.

End point type	Secondary

End point timeframe:

Day 1 of the Treatment Period (predose and postdose)

End point values	Serial Spirometry Subset:FS MDPI 200 / 12.5 mcg	Serial Spirometry Subset:FS MDPI 100 / 12.5 mcg	Serial Spirometry Subset: Fp MDPI 200 mcg	Serial Spirometry Subset: Fp MDPI 100 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	58	61	64
Units: hours				
median (confidence interval 95%)				
15% improvement	0.8 (0.31 to 1.77)	0.9 (0.48 to 11.96)	9999 (3.84 to 9999)	9999 (9999 to 9999)
12% improvement	0.4 (0.25 to 0.81)	0.4 (0.29 to 1.68)	6.9 (2.69 to 9999)	9999 (5.58 to 9999)

End point values	Serial Spirometry			

	Subset: Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: hours				
median (confidence interval 95%)				
15% improvement	9999 (9999 to 9999)			
12% improvement	9999 (5.68 to 9999)			

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. Relation 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 of the Treatment Period

End point values	Placebo MDPI	Fp MDPI 100 mcg	Fp MDPI 200 mcg	FS MDPI 100 / 12.5 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	144[49]	145[50]	146[51]	143[52]
Units: patients				
>=1 TEAE	52	53	60	59
>=1 severe TEAE	1	1	0	2
>=1 treatment-related TEAE	5	6	9	4
>=1 severe treatment-related TEAE	0	0	0	0
>=1 serious TEAE	1	1	1	2
>=1 TEAE leading to withdrawal	2	2	0	2
>=1 nonserious TEAE	52	52	60	58
>=1 TEAE resulting in death	0	0	0	1

Notes:

[49] - Safety population

[50] - Safety population

[51] - Safety population

[52] - Safety population

End point values	FS MDPI 200 / 12.5 mcg			
Subject group type	Reporting group			
Number of subjects analysed	145[53]			
Units: patients				
>=1 TEAE	61			
>=1 severe TEAE	3			
>=1 treatment-related TEAE	8			
>=1 severe treatment-related TEAE	1			
>=1 serious TEAE	2			
>=1 TEAE leading to withdrawal	2			
>=1 nonserious TEAE	61			
>=1 TEAE resulting in death	0			

Notes:

[53] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 14	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Placebo MDPI
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of placebo for 12 weeks.	
Reporting group title	Fp MDPI 100 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 200 mcg for 12 weeks.	
Reporting group title	Fp MDPI 200 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate for a total daily dose of 400 mcg for 12 weeks.	
Reporting group title	FS MDPI 100 / 12.5 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 100 mcg (for a total daily dose of 200 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks.	
Reporting group title	FS MDPI 200 / 12.5 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 200 mcg (for a total daily dose of 400 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) for 12 weeks.	

Serious adverse events	Placebo MDPI	Fp MDPI 100 mcg	Fp MDPI 200 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 144 (0.69%)	1 / 145 (0.69%)	1 / 146 (0.68%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	0 / 146 (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
Nervous system disorders			

Grand mal convulsion			
subjects affected / exposed	0 / 144 (0.00%)	1 / 145 (0.69%)	0 / 146 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	0 / 146 (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	1 / 144 (0.69%)	0 / 145 (0.00%)	0 / 146 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 144 (0.00%)	0 / 145 (0.00%)	0 / 146 (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

Serious adverse events	FS MDPI 100 / 12.5 mcg	FS MDPI 200 / 12.5 mcg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 143 (1.40%)	2 / 145 (1.38%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 143 (0.70%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	0 / 143 (0.00%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 143 (0.00%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 143 (0.70%)	0 / 145 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 143 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 145 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo MDPI	Fp MDPI 100 mcg	Fp MDPI 200 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 144 (13.89%)	26 / 145 (17.93%)	20 / 146 (13.70%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 144 (4.86%)	11 / 145 (7.59%)	7 / 146 (4.79%)
occurrences (all)	10	18	7

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 144 (5.56%)	7 / 145 (4.83%)	7 / 146 (4.79%)
occurrences (all)	9	7	8
Upper respiratory tract infection			
subjects affected / exposed	7 / 144 (4.86%)	9 / 145 (6.21%)	8 / 146 (5.48%)
occurrences (all)	7	11	9

Non-serious adverse events	FS MDPI 100 / 12.5 mcg	FS MDPI 200 / 12.5 mcg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 143 (14.69%)	20 / 145 (13.79%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 143 (4.20%)	4 / 145 (2.76%)	
occurrences (all)	21	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 143 (6.99%)	10 / 145 (6.90%)	
occurrences (all)	10	12	
Upper respiratory tract infection			
subjects affected / exposed	6 / 143 (4.20%)	6 / 145 (4.14%)	
occurrences (all)	6	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2014	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.
10 December 2014	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.
19 February 2015	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. • The determination of potentially exclusionary ECG findings was clarified.
09 April 2015	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 FEV1 was changed from over the 12-week treatment period to at week 12 (TV9), and the primary endpoint for serial spirometry was specified as standardized baseline-adjusted FEV1 AUEC0-12h 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported