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

Summary

EudraCT number	2014-001149-25
Trial protocol	CZ PL HU
Global end of trial date	21 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-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02139644
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, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, 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	15 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 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 fluticasone propionate multidose dry powder inhaler (Fp MDPI) and fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler (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	25 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	Poland: 107
Country: Number of subjects enrolled	Hungary: 68
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Russian Federation: 94
Country: Number of subjects enrolled	Ukraine: 43
Country: Number of subjects enrolled	United States: 456

Country: Number of subjects enrolled	South Africa: 16
Worldwide total number of subjects	787
EEA total number of subjects	175

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)	112
Adults (18-64 years)	595
From 65 to 84 years	79
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 1363 patients with persistent asthma were screened for enrollment into this study. Of the 787 patients enrolled, 140 were not randomized, most commonly (70 patients) because of not meeting randomization criteria.

Pre-assignment

Screening details:

787 patients at 129 investigational centers in the US and elsewhere internationally met entry criteria and were considered eligible for enrollment into the study.

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:

Patients discontinued their current inhaled corticosteroid and instead took 1 inhalation twice a day of a single-blinded placebo multidose dry powder inhaler (MDPI) device and 1 puff twice a day of an open-label QVAR® (beclomethasone dipropionate 40 mcg metered-dose inhaler, or equivalent). Placebo, manufactured by Teva, was supplied in a MDPI device that was identical to the devices used to deliver active drug, and indistinguishable from the active treatments.

Arms

Arm title	Enrolled Patients

Arm description:

During the run-in period (from the screening visit to the randomization visit), all patients replaced their current rescue medication with study-specific rescue medication (albuterol/salbutamol HFA MDI) for use on an as-needed basis for the immediate relief of asthma symptoms throughout the period. All patients discontinued their current ICS or ICS/LABA, and took 1 inhalation twice a day from a single-blinded placebo MDPI device and 1 puff twice a day from open-label QVAR 40 mcg HFA MDI (or equivalent).

Arm type	Active comparator
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. Albuterol/salmeterol HFA MDI was supplied to all patients for use as rescue medication throughout the run-in and treatment periods.

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

Dosage and administration details:

Placebo administered via a multidose dry powder inhaler (MDPI) one puff in the morning and one puff in the evening for the duration of the Run-in Period (14-21 days).

Investigational medicinal product name	Beclomethasone dipropionate
Investigational medicinal product code	
Other name	QVAR
Pharmaceutical forms	Inhalation solution

Routes of administration	Inhalation use

Dosage and administration details:

QVAR (beclomethasone dipropionate) 40 mcg Inhalation Aerosol is a pressurized MDI that contains a Food and Drug Administration (FDA)-approved formulation of beclomethasone dipropionate. Patients took 1 puff twice a day from open-label QVAR 40 mcg hydrofluoroalkane (specifically, HFA-134a) metered-dose inhaler (MDI). A clinically equivalent dose of inhaled corticosteroid (ICS) was substituted in countries where QVAR 40 mcg was not available.

Number of subjects in period 1	Enrolled Patients
Started	787
Completed	647
Not completed	140
Exclusion criteria met	11
Consent withdrawn by subject	12
Adverse event, non-fatal	3
Randomization criteria not met	70
Lost to follow-up	8
Inclusion criteria not met	30
not specified	6

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 randomized 1:1:1:1:1 to receive Fp MDPI 50 mcg, Fp MDPI 100 mcg, FS MDPI 50/12.5 mcg, FS MDPI 100/12.5 mcg, or placebo MDPI for the entire treatment period. Patients and investigators remained blinded to treatment assignment during the study.
The sponsor’s clinical personnel involved in the study were also blinded to the study drug identity until the database was locked for analysis and the treatment assignment revealed.

Arms

Are arms mutually exclusive?	Yes
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.

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.

Arm title	FS MDPI 50 / 12.5 mcg

Arm description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 50 mcg (for a total daily dose of 100 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 50 mcg in the morning and evening for a total daily dose of 100 mcg.

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.

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 100 mcg in the morning and evening for a total daily dose of 200 mcg.

Arm title	Fp MDPI 50 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 100 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 50 mcg in the morning and evening for a total daily dose of 100 mcg.

Arm title	Placebo MDPI

Arm description:

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).

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

Dosage and administration details:

Placebo administered via a multidose dry powder inhaler (MDPI) one puff in the morning and one puff in the evening for12 weeks.

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]	FS MDPI 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg
Started	129	129	130
Intent to treat population	129	129	130
Safety population	126	128	129
Full analysis set	126	128	129
Completed	126	121	121
Not completed	3	8	9
Consent withdrawn by subject	-	2	2
Disease progression	-	-	1
Randomized but not treated	3	1	1
Adverse event, non-fatal	-	3	2
Non-compliance	-	-	1
Lost to follow-up	-	1	1
Lack of efficacy	-	1	-
Protocol deviation	-	-	1

Number of subjects in period 2[2]	Fp MDPI 50 mcg	Placebo MDPI
Started	129	130
Intent to treat population	129	130
Safety population	129	129
Full analysis set	128	129
Completed	121	113
Not completed	8	17
Consent withdrawn by subject	3	2
Disease progression	1	2
Randomized but not treated	-	1
Adverse event, non-fatal	1	6
Non-compliance	-	-
Lost to follow-up	1	1
Lack of efficacy	1	4
Protocol deviation	1	1

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	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 50 / 12.5 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 50 mcg (for a total daily dose of 100 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) 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 50 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 100 mcg for 12 weeks.	
Reporting group title	Placebo MDPI
Reporting group description:	
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).	

Reporting group values	FS MDPI 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg
Number of subjects	129	129	130
Age categorical			
ITT population			
Units: Subjects			
Adolescents (12-17 years)	19	19	18
Adults (18-64 years)	100	97	102
65+ years	10	13	10
Age continuous			
ITT population			
Units: years			
arithmetic mean	41	41.4	40.6
standard deviation	± 17	± 18.61	± 17.16
Gender categorical			
ITT population			
Units: Subjects			
Female	72	71	76
Male	57	58	54
Race			
ITT population			
Units: Subjects			
White	105	109	93
Black or African American	20	19	30
Asian	4	1	4

American Indian or Alaska Native	0	0	1
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	2
Ethnicity			
ITT population			
Units: Subjects			
Not Hispanic or Latino	119	121	114
Hispanic or Latino	10	8	16
Unknown	0	0	0
History of smoking			
ITT population			
Units: Subjects			
Prior smoker	18	13	15
No tobacco use	111	116	115
Previous Asthma Therapy			
ITT population			
Units: Subjects			
Inhaled corticosteroid	97	90	83
Inhaled corticosteroid/long-acting beta2-agonist	32	39	47
Body Mass Index			
ITT population			
Units: kg/m^2			
arithmetic mean	27.94	28	27.63
standard deviation	± 6.686	± 7.166	± 6.603
Forced Expiratory Volume in 1 second (FEV1)			
ITT population (n=126, 128, 129, 129, 129)			
Units: liters			
arithmetic mean	2.162	2.302	2.166
standard deviation	± 0.5522	± 0.6526	± 0.5725

Reporting group values	Fp MDPI 50 mcg	Placebo MDPI	Total
Number of subjects	129	130	647
Age categorical			
ITT population			
Units: Subjects			
Adolescents (12-17 years)	13	17	86
Adults (18-64 years)	93	102	494
65+ years	23	11	67
Age continuous			
ITT population			
Units: years			
arithmetic mean	43.3	40.9	
standard deviation	± 17.96	± 17.35	-
Gender categorical			
ITT population			
Units: Subjects			
Female	75	70	364
Male	54	60	283

Race			
ITT population			
Units: Subjects			
White	107	101	515
Black or African American	18	26	113
Asian	1	1	11
American Indian or Alaska Native	0	0	1
Native Hawaiian or other Pacific Islander	1	0	1
Other	2	2	6
Ethnicity			
ITT population			
Units: Subjects			
Not Hispanic or Latino	121	122	597
Hispanic or Latino	8	7	49
Unknown	0	1	1
History of smoking			
ITT population			
Units: Subjects			
Prior smoker	14	12	72
No tobacco use	115	118	575
Previous Asthma Therapy			
ITT population			
Units: Subjects			
Inhaled corticosteroid	89	102	461
Inhaled corticosteroid/long-acting beta2-agonist	40	28	186
Body Mass Index			
ITT population			
Units: kg/m^2			
arithmetic mean	27.94	27.99	
standard deviation	± 7.259	± 6.849	-
Forced Expiratory Volume in 1 second (FEV1)			
ITT population (n=126, 128, 129, 129, 129)			
Units: liters			
arithmetic mean	2.132	2.188	
standard deviation	± 0.6341	± 0.5628	-

End points

End points reporting groups

Reporting group title	Enrolled Patients

Reporting group description:

During the run-in period (from the screening visit to the randomization visit), all patients replaced their current rescue medication with study-specific rescue medication (albuterol/salbutamol HFA MDI) for use on an as-needed basis for the immediate relief of asthma symptoms throughout the period. All patients discontinued their current ICS or ICS/LABA, and took 1 inhalation twice a day from a single-blinded placebo MDPI device and 1 puff twice a day from open-label QVAR 40 mcg HFA MDI (or equivalent).

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 50 / 12.5 mcg

Reporting group description:

Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 50 mcg (for a total daily dose of 100 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) 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 50 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 100 mcg for 12 weeks.

Reporting group title	Placebo MDPI

Reporting group description:

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).

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:FS MDPI 50 / 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 50 mcg and salmeterol 12.5 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: Fp MDPI 50 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 50 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 AUEC0-12h) 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 AUEC0-12h) at Week 12

End point description:

A subset of approximately 300 patients who performed postdose serial spirometry is based on sample size calculation. 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 100 / 12.5 mcg	Serial Spirometry Subset:FS MDPI 50 / 12.5 mcg	Serial Spirometry Subset: Fp MDPI 100 mcg	Serial Spirometry Subset: Fp MDPI 50 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61[1]	56[2]	72[3]	63[4]
Units: liters				
least squares mean (standard error)	0.408 (± 0.0465)	0.399 (± 0.0479)	0.254 (± 0.0434)	0.268 (± 0.0457)

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

End point values	Serial Spirometry Subset: Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	60[5]			
Units: liters				
least squares mean (standard error)	0.074 (± 0.0487)			

Notes:

[5] - FAS

Statistical analyses

Statistical analysis title	AUEC0-12h: 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 first 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	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0076 [6]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.154
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.041
upper limit	0.267

Notes:

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

Statistical analysis title	AUEC0-12h: FS 50/12.5 vs Fp 50 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 50 / 12.5 mcg v Serial Spirometry Subset: Fp MDPI 50 mcg
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0322 [7]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.25

Notes:

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

Statistical analysis title	AUEC0-12h: FS 100/12.5 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 100 / 12.5 mcg v Serial Spirometry Subset: Placebo MDPI

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [8]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.335
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.216
upper limit	0.453

Notes:

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

Statistical analysis title	AUEC0-12h: FS 50/12.5 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 50 / 12.5 mcg v Serial Spirometry Subset: Placebo MDPI
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [9]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.325
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.203
upper limit	0.447

Notes:

[9] - 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 was 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 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg	Fp MDPI 50 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126[10]	128[11]	129[12]	128[13]
Units: liters				
least squares mean (standard error)	0.315 (± 0.0352)	0.319 (± 0.035)	0.204 (± 0.034)	0.172 (± 0.0347)

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

[13] - FAS

End point values	Placebo MDPI			
Subject group type	Reporting group			
Number of subjects analysed	129[14]			
Units: liters				
least squares mean (standard error)	0.053 (± 0.035)			

Notes:

[14] - FAS

Statistical analyses

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 fifth in the sequence.

Comparison groups	FS MDPI 100 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [15]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.262
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.168
upper limit	0.356

Notes:

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

Statistical analysis title	FEV1: FS 50/12.5 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 50 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [16]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.266
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.172
upper limit	0.36

Notes:

[16] - 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 seventh in the sequence.

Comparison groups	Fp MDPI 100 mcg v Placebo MDPI
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017 [17]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	0.244

Notes:

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

Statistical analysis title	FEV1: Fp 50 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 50 mcg v Placebo MDPI
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0132 [18]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.119

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.212

Notes:

[18] - 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), Day 1 (postdose) daily until Week 12

End point values	FS MDPI 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg	Fp MDPI 50 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125[19]	128[20]	129[21]	128[22]
Units: liters / minute				
least squares mean (standard error)	24.415 (± 3.153)	24.864 (± 3.1182)	14.517 (± 3.0778)	10.609 (± 3.1176)

Notes:

[19] - FAS

[20] - FAS

[21] - FAS

[22] - FAS

End point values	Placebo MDPI			
Subject group type	Reporting group			
Number of subjects analysed	128[23]			
Units: liters / minute				
least squares mean (standard error)	3.591 (± 3.1474)			

Notes:

[23] - FAS

Statistical analyses

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	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123 [24]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	10.926
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.38
upper limit	19.471

Notes:

[24] - Significance level of 0.05.

Statistical analysis title	AM PEF: Fp 50 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 50 mcg v Placebo MDPI
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1074 [25]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	7.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.531
upper limit	15.567

Notes:

[25] - 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	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [26]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	20.824
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.253
upper limit	29.395

Notes:

[26] - Significance level of 0.05.

Statistical analysis title	AM PEF: FS 50/12.5 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 50 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [27]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	21.273
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.728
upper limit	29.818

Notes:

[27] - 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	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0233 [28]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	9.898

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.349
upper limit	18.447

Notes:

[28] - Significance level of 0.05.

Statistical analysis title	AM PEF: FS 50/12.5 mcg vs FP 50 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 50 / 12.5 mcg v Fp MDPI 50 mcg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [29]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	14.255
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.732
upper limit	22.778

Notes:

[29] - Significance level of 0.05.

Statistical analysis title	AM PEF: FS 50/12.5 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 50 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0175 [30]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	10.347
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.822
upper limit	18.872

Notes:

[30] - 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 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg	Fp MDPI 50 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125[31]	128[32]	129[33]	128[34]
Units: units on a scale				
least squares mean (standard error)	-0.364 (± 0.0318)	-0.329 (± 0.0314)	-0.3 (± 0.0308)	-0.278 (± 0.0314)

Notes:

[31] - FAS

[32] - FAS

[33] - FAS

[34] - FAS

End point values	Placebo MDPI			
Subject group type	Reporting group			
Number of subjects analysed	128[35]			
Units: units on a scale				
least squares mean (standard error)	-0.135 (± 0.0318)			

Notes:

[35] - FAS

Statistical analyses

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	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [36]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.251
upper limit	-0.08

Notes:

[36] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: Fp 50 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 50 mcg v Placebo MDPI
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [37]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.229
upper limit	-0.058

Notes:

[37] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 100/12.5 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	253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [38]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.315
upper limit	-0.144

Notes:

[38] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 50/12.5 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 50 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [39]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.279
upper limit	-0.109

Notes:

[39] - 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	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1381 [40]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.064

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.021

Notes:

[40] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 50/12.5 mcg vs Fp 50 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 50 / 12.5 mcg v Fp MDPI 50 mcg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2438 [41]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.136
upper limit	0.035

Notes:

[41] - Significance level of 0.05.

Statistical analysis title	Asthma Symptoms: FS 50/12.5 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 50 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5095 [42]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.114
upper limit	0.057

Notes:

[42] - 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 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg	Fp MDPI 50 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126[43]	128[44]	129[45]	128[46]
Units: puffs				
least squares mean (standard error)	-0.677 (± 0.0937)	-0.706 (± 0.093)	-0.466 (± 0.0915)	-0.467 (± 0.0928)

Notes:

[43] - FAS

[44] - FAS

[45] - FAS

[46] - FAS

End point values	Placebo MDPI			
Subject group type	Reporting group			
Number of subjects analysed	129[47]			
Units: puffs				
least squares mean (standard error)	-0.003 (± 0.0937)			

Notes:

[47] - FAS

Statistical analyses

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	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [48]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.463
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.716
upper limit	-0.209

Notes:

[48] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: Fp 50 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 50 mcg v Placebo MDPI
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [49]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.464
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.718
upper limit	-0.211

Notes:

[49] - 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	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [50]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.675

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.928
upper limit	-0.421

Notes:

[50] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: FS 50/12.5 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 50 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [51]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.704
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.957
upper limit	-0.45

Notes:

[51] - 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	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1014 [52]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.212
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.465
upper limit	0.042

Notes:

[52] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: FS 50/12.5 mcg vs Fp 50 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 50 / 12.5 mcg v Fp MDPI 50 mcg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064 [53]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.239
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.492
upper limit	0.014

Notes:

[53] - Significance level of 0.05.

Statistical analysis title	Rescue Meds: FS 50/12.5 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 50 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0626 [54]
Method	mixed model for repeated measures
Parameter estimate	LSM difference
Point estimate	-0.241
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.494
upper limit	0.013

Notes:

[54] - 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 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg	Fp MDPI 50 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126[55]	128[56]	129[57]	128[58]
Units: probability				
number (confidence interval 95%)	1 (1 to 1)	0.9917 (0.942 to 0.999)	0.9919 (0.944 to 0.999)	0.9919 (0.944 to 0.999)

Notes:

[55] - FAS

[56] - FAS

[57] - FAS

[58] - FAS

End point values	Placebo MDPI			
Subject group type	Reporting group			
Number of subjects analysed	129[59]			
Units: probability				
number (confidence interval 95%)	0.9681 (0.917 to 0.988)			

Notes:

[59] - FAS

Statistical analyses

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	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1679 [60]
Method	Logrank

Notes:

[60] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: Fp 50 mcg vs Placebo
Comparison groups	Fp MDPI 50 mcg v Placebo MDPI
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1701 [61]
Method	Logrank

Notes:

[61] - 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	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0437 [62]
Method	Logrank

Notes:

[62] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FS 50/12.5 mcg vs Placebo
Comparison groups	FS MDPI 50 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1718 [63]
Method	Logrank

Notes:

[63] - 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	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3134 [64]
Method	Logrank

Notes:

[64] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FS 50/12.5 mcg vs Fp 50 mcg
Comparison groups	FS MDPI 50 / 12.5 mcg v Fp MDPI 50 mcg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.993 [65]
Method	Logrank

Notes:

[65] - Significance level of 0.05.

Statistical analysis title	Probability 12 Weeks: FS 50/12.5 mcg vs Fp100 mcg
Comparison groups	FS MDPI 50 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9999 [66]
Method	Logrank

Notes:

[66] - 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 of 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 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg	Fp MDPI 50 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109[67]	102[68]	103[69]	108[70]
Units: units on a scale				
least squares mean (standard error)	0.808 (± 0.0728)	0.565 (± 0.0752)	0.636 (± 0.0736)	0.588 (± 0.0733)

Notes:

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

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

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

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

End point values	Placebo MDPI			
Subject group type	Reporting group			
Number of subjects analysed	97[71]			
Units: units on a scale				
least squares mean (standard error)	0.335 (± 0.0777)			

Notes:

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

Statistical analyses

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	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044 [72]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.301
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.508

Notes:

[72] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): Fp 50 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 50 mcg v Placebo MDPI
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0155 [73]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.253
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.048
upper limit	0.458

Notes:

[73] - 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	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [74]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.473

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.676

Notes:

[74] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): FS 50/12.5 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 50 / 12.5 mcg v Placebo MDPI
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0293 [75]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.437

Notes:

[75] - 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	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0913 [76]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	0.172
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.372

Notes:

[76] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): FS 50/12.5 mcg vs Fp 50 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 50 / 12.5 mcg v Fp MDPI 50 mcg
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8216 [77]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.223
upper limit	0.177

Notes:

[77] - Significance level of 0.05.

Statistical analysis title	AQLQ(S): FS 50/12.5 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 50 / 12.5 mcg v Fp MDPI 100 mcg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4934 [78]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.275
upper limit	0.133

Notes:

[78] - 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:

A subset of approximately 300 patients who performed postdose serial spirometry is based on sample size calculation.
Baseline FEV1 was the average of 2 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,

baseline 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 100 / 12.5 mcg	Serial Spirometry Subset:FS MDPI 50 / 12.5 mcg	Serial Spirometry Subset: Fp MDPI 100 mcg	Serial Spirometry Subset: Fp MDPI 50 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61[79]	56[80]	72[81]	63[82]
Units: hours				
median (confidence interval 95%)				
15% improvement	4.3 (1.07 to 9999)	1.3 (0.6 to 2.75)	9999 (10.19 to 9999)	9999 (9999 to 9999)
12% improvement	1 (0.46 to 3.72)	0.5 (0.3 to 1.55)	9999 (7.36 to 9999)	9999 (3.89 to 9999)

Notes:

[79] - FAS

[80] - FAS

[81] - FAS

[82] - FAS

End point values	Serial Spirometry Subset: Placebo MDPI			
Subject group type	Subject analysis set			
Number of subjects analysed	60[83]			
Units: hours				
median (confidence interval 95%)				
15% improvement	9999 (9999 to 9999)			
12% improvement	9999 (7.27 to 9999)			

Notes:

[83] - FAS

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 of the Treatment Period

End point values	FS MDPI 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg	Fp MDPI 50 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126[84]	128[85]	129[86]	129[87]
Units: patients				
>=1 TEAE	37	46	40	44
>=1 severe TEAE	2	0	1	1
>=1 treatment-related TEAE	4	4	5	7
>=1 severe treatment-related TEAE	0	0	0	0
>=1 serious TEAE	1	0	1	0
>=1 TEAE leading to withdrawal	0	3	2	1
>=1 nonserious TEAE	36	46	39	44
>=1 TEAE resulting in death	0	0	0	0

Notes:

[84] - Safety population

[85] - Safety population

[86] - Safety population

[87] - Safety population

End point values	Placebo MDPI			
Subject group type	Reporting group			
Number of subjects analysed	129[88]			
Units: patients				
>=1 TEAE	47			
>=1 severe TEAE	0			
>=1 treatment-related TEAE	5			
>=1 severe treatment-related TEAE	0			
>=1 serious TEAE	2			
>=1 TEAE leading to withdrawal	6			
>=1 nonserious TEAE	45			
>=1 TEAE resulting in death	0			

Notes:

[88] - 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 12	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
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 50 / 12.5 mcg
Reporting group description:	
Patients took 1 inhalation using a multidose dry powder inhaler (MDPI) twice a day of fluticasone propionate 50 mcg (for a total daily dose of 100 mcg) and salmeterol 12.5 mcg (for a total daily dose of 25 mcg) 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 50 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 100 mcg for 12 weeks.	
Reporting group title	Placebo MDPI
Reporting group description:	
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).	

Serious adverse events	FS MDPI 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	1 / 129 (0.78%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 128 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal			

conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 126 (0.00%)	0 / 128 (0.00%)	0 / 129 (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
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	0 / 129 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	0 / 129 (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
Cholecystitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	0 / 129 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 128 (0.00%)	0 / 129 (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	Fp MDPI 50 mcg	Placebo MDPI	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 129 (0.00%)	2 / 129 (1.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 129 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 129 (0.78%)	
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	FS MDPI 100 / 12.5 mcg	FS MDPI 50 / 12.5 mcg	Fp MDPI 100 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 126 (9.52%)	22 / 128 (17.19%)	21 / 129 (16.28%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 126 (5.56%)	7 / 128 (5.47%)	9 / 129 (6.98%)
occurrences (all)	10	8	11
Infections and infestations			

Upper respiratory tract infection			
subjects affected / exposed	2 / 126 (1.59%)	6 / 128 (4.69%)	4 / 129 (3.10%)
occurrences (all)	2	6	4
Nasopharyngitis			
subjects affected / exposed	3 / 126 (2.38%)	11 / 128 (8.59%)	9 / 129 (6.98%)
occurrences (all)	3	11	10

Non-serious adverse events	Fp MDPI 50 mcg	Placebo MDPI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 129 (11.63%)	15 / 129 (11.63%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 129 (1.55%)	5 / 129 (3.88%)	
occurrences (all)	4	7	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 129 (5.43%)	6 / 129 (4.65%)	
occurrences (all)	8	6	
Nasopharyngitis			
subjects affected / exposed	7 / 129 (5.43%)	4 / 129 (3.10%)	
occurrences (all)	8	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2014	Amendment 1 (dated 17 November 2014) to the protocol was issued when 115 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 primary endpoint was changed from change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV1 over the 12-week treatment period to standardized baseline-adjusted FEV1 AUEC0-12wk. Sample size, power, and statistical considerations were updated. • 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. • The number of anticipated sites was increased from 80 to 200.
19 February 2015	Amendment 2 (dated 19 February 2015) to the protocol was issued when 309 patients had been enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: • The inclusion criteria were modified to allow patients on mid-dose ICS therapy to participate in the study (in addition to those on low-dose ICS therapy already included in the study). • The determination of potentially exclusionary ECG findings was clarified.
14 July 2015	Amendment 3 (dated 14 July 2015) to the protocol was issued when 647 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 primary endpoint was changed from standardized change from baseline-adjusted trough (AM predose and pre-rescue bronchodilator) FEV1 AUEC0-12wk at week 12 to change from baseline in trough (AM predose and pre-rescue bronchodilator) FEV1 at week 12. • As recommended by the US FDA, the CPRA graph was added to examine all possible response levels of interest. • Related to the change in the primary endpoint, the method for its analysis was 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. • Specific secondary efficacy endpoints were changed to other efficacy endpoints, and the sequential orders of secondary and other endpoints were changed. • The analyses of the AQLQ(S) and PAQLQ(S) were separated. • 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