



Clinical trial results:

A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared with Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler in Patients Aged 4 Through 11 Years With Persistent Asthma

Summary

EudraCT number	2016-003835-39
Trial protocol	HU
Global end of trial date	13 April 2019

Results information

Result version number	v1 (current)
This version publication date	24 October 2019
First version publication date	24 October 2019

Trial information

Trial identification

Sponsor protocol code	FSS-AS-30003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02980133
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc.
Sponsor organisation address	41 Moores Road, Frazer, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 8884838279, info.eraclinical@teva.de

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	14 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2019
Global end of trial reached?	Yes
Global end of trial date	13 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of fluticasone propionate (Fp) multidose dry powder inhaler (MDPI) and fluticasone propionate/salmeterol (FS) MDPI when administered over 12 weeks in participants of 4 through 11 years of age with persistent asthma.

Protection of trial subjects:

This study was conducted in full accordance with the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6 and any applicable national and local laws and regulations (for example; Title 21 Code of Federal Regulations Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 December 2016
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	Georgia: 43
Country: Number of subjects enrolled	Hungary: 84
Country: Number of subjects enrolled	Russian Federation: 71
Country: Number of subjects enrolled	Ukraine: 150
Country: Number of subjects enrolled	United States: 493
Worldwide total number of subjects	841
EEA total number of subjects	84

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)	841
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 841 participants with persistent asthma were randomized in a 1:1:1:1 ratio to receive Fp MDPI 25 micrograms (mcg), Fp MDPI 50 mcg, FS MDPI 50/12.5 mcg, or placebo MDPI. Randomization was stratified by previous therapy (inhaled corticosteroid [ICS] or non-corticosteroid [NCS]).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo MDPI

Arm description:

Participants received matching placebo via MDPI 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:

Matching placebo was administered via MDPI per the schedule specified in the arm.

Arm title	Fp MDPI 25 mcg BID
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Arm description:

Participants received 1 inhalation of 25 mcg fluticasone propionate (Fp) via MDPI twice daily (BID) (total daily dose: 50 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 was administered via MDPI per the dose and schedule specified in the arm.

Arm title	Fp MDPI 50 mcg BID
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Arm description:

Participants received 1 inhalation of 50 mcg fluticasone propionate via MDPI BID (total daily dose: 100 mcg) for 12 weeks.

Arm type	Experimental
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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 was administered via MDPI per the dose and schedule specified in the arm.	
Arm title	FS MDPI 50/12.5 mcg BID

Arm description:

Participants received 1 inhalation of 50/12.5 mcg fluticasone propionate/salmeterol (FS) via MDPI BID (total daily dose: 100/25 mcg) for 12 weeks.

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

Dosage and administration details:

Fluticasone propionate/salmeterol was administered via MDPI per the dose and schedule specified in the arm.

Number of subjects in period 1	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID
Started	209	211	210
Received at least 1 dose of study drug	209	211	208
Completed	202	206	203
Not completed	7	5	7
Consent withdrawn by subject	-	-	1
Other than specified	1	1	2
Lost to follow-up	-	-	1
Withdrawal by parent/guardian	6	3	3
Protocol deviation	-	1	-

Number of subjects in period 1	FS MDPI 50/12.5 mcg BID
Started	211
Received at least 1 dose of study drug	211
Completed	205
Not completed	6
Consent withdrawn by subject	-
Other than specified	2
Lost to follow-up	3
Withdrawal by parent/guardian	1
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo MDPI
Reporting group description: Participants received matching placebo via MDPI for 12 weeks.	
Reporting group title	Fp MDPI 25 mcg BID
Reporting group description: Participants received 1 inhalation of 25 mcg fluticasone propionate (Fp) via MDPI twice daily (BID) (total daily dose: 50 mcg) for 12 weeks.	
Reporting group title	Fp MDPI 50 mcg BID
Reporting group description: Participants received 1 inhalation of 50 mcg fluticasone propionate via MDPI BID (total daily dose: 100 mcg) for 12 weeks.	
Reporting group title	FS MDPI 50/12.5 mcg BID
Reporting group description: Participants received 1 inhalation of 50/12.5 mcg fluticasone propionate/salmeterol (FS) via MDPI BID (total daily dose: 100/25 mcg) for 12 weeks.	

Reporting group values	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID
Number of subjects	209	211	210
Age categorical Units: Subjects			
Children (2-11 years)	209	211	210
Age Continuous Units: years			
arithmetic mean	8.5	8.7	8.5
standard deviation	± 1.98	± 1.83	± 1.94
Sex: Female, Male Units: Subjects			
Female	79	74	80
Male	130	137	130
Race/Ethnicity, Customized Units: Subjects			
White	172	168	171
Black or African American	33	41	32
Asian	1	0	2
American Indian or Alaska Native	0	1	2
Native Hawaiian or Other Pacific Islander	1	0	0
Other	2	1	3
Percent Predicted Forced Expiratory Volume in 1 Second (FEV1)			
FEV1 is the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Baseline trough morning percent predicted FEV1 was defined as the average value of recorded (nonmissing) morning assessments 5 out of the last 7 days prior to randomization. 'Number of participants analyzed' for this parameter are 209, 211, 209, and 211 for each arm respectively.			
Units: percent predicted of FEV1			
arithmetic mean	68.8	69.6	69.6
standard deviation	± 9.70	± 9.68	± 9.47
1-Hour Postdose Percent Predicted			

Morning FEV1			
FEV1 is the volume of air exhaled in the first second of a forced expiration as measured by spirometer. The baseline 1-hour trough morning percent predicted FEV1 was defined as the predose trough morning percent predicted FEV1 measurement at the randomization visit (Baseline [Day 1]) at the investigational center. 'Number of participants analyzed' for this parameter are 205, 209, 207, and 211 for each arm respectively.			
Units: percent predicted of FEV1			
arithmetic mean	81.1	79.3	80.2
standard deviation	± 16.92	± 14.60	± 15.87

Reporting group values	FS MDPI 50/12.5 mcg BID	Total	
Number of subjects	211	841	
Age categorical			
Units: Subjects			
Children (2-11 years)	211	841	
Age Continuous			
Units: years			
arithmetic mean	8.4	-	
standard deviation	± 2.05	-	
Sex: Female, Male			
Units: Subjects			
Female	91	324	
Male	120	517	
Race/Ethnicity, Customized			
Units: Subjects			
White	172	683	
Black or African American	29	135	
Asian	3	6	
American Indian or Alaska Native	0	3	
Native Hawaiian or Other Pacific Islander	0	1	
Other	7	13	
Percent Predicted Forced Expiratory Volume in 1 Second (FEV1)			
FEV1 is the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Baseline trough morning percent predicted FEV1 was defined as the average value of recorded (nonmissing) morning assessments 5 out of the last 7 days prior to randomization. 'Number of participants analyzed' for this parameter are 209, 211, 209, and 211 for each arm respectively.			
Units: percent predicted of FEV1			
arithmetic mean	69.9	-	
standard deviation	± 9.15	-	
1-Hour Postdose Percent Predicted Morning FEV1			
FEV1 is the volume of air exhaled in the first second of a forced expiration as measured by spirometer. The baseline 1-hour trough morning percent predicted FEV1 was defined as the predose trough morning percent predicted FEV1 measurement at the randomization visit (Baseline [Day 1]) at the investigational center. 'Number of participants analyzed' for this parameter are 205, 209, 207, and 211 for each arm respectively.			
Units: percent predicted of FEV1			
arithmetic mean	87.3	-	
standard deviation	± 18.72	-	

End points

End points reporting groups

Reporting group title	Placebo MDPI
Reporting group description: Participants received matching placebo via MDPI for 12 weeks.	
Reporting group title	Fp MDPI 25 mcg BID
Reporting group description: Participants received 1 inhalation of 25 mcg fluticasone propionate (Fp) via MDPI twice daily (BID) (total daily dose: 50 mcg) for 12 weeks.	
Reporting group title	Fp MDPI 50 mcg BID
Reporting group description: Participants received 1 inhalation of 50 mcg fluticasone propionate via MDPI BID (total daily dose: 100 mcg) for 12 weeks.	
Reporting group title	FS MDPI 50/12.5 mcg BID
Reporting group description: Participants received 1 inhalation of 50/12.5 mcg fluticasone propionate/salmeterol (FS) via MDPI BID (total daily dose: 100/25 mcg) for 12 weeks.	

Primary: For FS MDPI Versus Fp MDPI: Change From Baseline in 1-Hour Postdose Percent Predicted Morning Forced Expiratory Volume in 1 Second (FEV1) at Week 12

End point title	For FS MDPI Versus Fp MDPI: Change From Baseline in 1-Hour Postdose Percent Predicted Morning Forced Expiratory Volume in 1 Second (FEV1) at Week 12 ^[1]
End point description: FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. The baseline 1-hour trough morning percent predicted FEV1 was defined as the predose trough morning percent predicted FEV1 measurement at the randomization visit (Baseline [Day 1]) at the investigational center. The IMP dose was administered right after the predose FEV1 measurement (within a 10 minute window). Participant then performed 1-hour (± 10 minutes) postdose lung function assessments on Week 12 at the investigational center. ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint. Missing data was imputed using missing not at random (MNAR) methodology for prematurely discontinued participants or missing at random (MAR) for completers with implausible data.	
End point type	Primary
End point timeframe: Baseline, Week 12	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is reporting statistics for the specified arms only.

End point values	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID	FS MDPI 50/12.5 mcg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	211	209	211	
Units: percent predicted of FEV1				
least squares mean (standard error)	16.8 (± 1.32)	16.4 (± 1.32)	18.2 (± 1.29)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using an analysis of covariance (ANCOVA) model with effects due to baseline trough morning percent predicted FEV1, sex, age, (pooled) investigational center, previous therapy (inhaled corticosteroid [ICS] or noncorticosteroid [NCS]), and investigational medicinal product (IMP) treatment group.	
Comparison groups	Fp MDPI 50 mcg BID v FS MDPI 50/12.5 mcg BID
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.285 ^[2]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	5.3

Notes:

[2] - Threshold for significance at 0.05 level.

Primary: For Fp MDPI Versus Placebo: Change From Baseline in Weekly Average of the Percent Predicted Trough Morning FEV1 at Week 12

End point title	For Fp MDPI Versus Placebo: Change From Baseline in Weekly Average of the Percent Predicted Trough Morning FEV1 at Week 12 ^[3]
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End point description:

Baseline trough morning percent predicted FEV1: the average value of recorded morning assessments 5 out of the last 7 days prior to randomization. First day before randomization consisted of electronic diary entry at home on the morning of randomization visit (Baseline [Day 1]) and the first day postrandomization consisted of electronic diary entry at home on the morning of the day after the randomization visit. For postdose weekly average of trough morning percent predicted FEV1 measurements, values were the averages based on the available data for that week. Averages were calculated as the sum of morning FEV1 values divided by number of nonmissing assessments. ITT analysis set: all randomized participants. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint. Missing data was imputed using MNAR methodology for prematurely discontinued participants or MAR for completers with implausible data.

End point type	Primary
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End point timeframe:

Baseline, Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is reporting statistics for the specified arms only.

End point values	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	209	211	209	
Units: percent predicted of FEV1				
least squares mean (standard error)	7.3 (± 1.10)	13.3 (± 1.09)	14.2 (± 1.10)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Analysis was performed using an ANCOVA model with effects due to baseline trough morning percent predicted FEV1, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), and IMP treatment group.	
Comparison groups	Placebo MDPI v Fp MDPI 25 mcg BID
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[4]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	8.8

Notes:

[4] - Threshold for significance at 0.05 level.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Analysis was performed using an ANCOVA model with effects due to baseline trough morning percent predicted FEV1, sex, age, (pooled) investigational center, previous therapy (ICS or NCS), and IMP treatment group.	
Comparison groups	Placebo MDPI v Fp MDPI 50 mcg BID
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[5]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.1
upper limit	9.8

Notes:

[5] - Threshold for significance at 0.05 level.

Secondary: Change From Baseline in the Weekly Average of Daily Trough Morning

(Predose and Pre-Rescue Bronchodilator) Peak Expiratory Flow (PEF) Over the 12 Week Treatment Period

End point title	Change From Baseline in the Weekly Average of Daily Trough Morning (Predose and Pre-Rescue Bronchodilator) Peak Expiratory Flow (PEF) Over the 12 Week Treatment Period
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End point description:

Morning PEF was determined in the morning, before administration of IMP or rescue medications. Baseline trough morning PEF was defined as the average value of recorded (nonmissing) morning assessments 5 out of the last 7 days prior to randomization. The first day before randomization consisted of the electronic participant diary entry at home on the morning of the randomization visit (Baseline [Day 1]) and the first day postrandomization consisted of the electronic participant diary entry at home on the morning of the day after the randomization visit (Baseline [Day 1]). For postdose weekly average of trough morning PEF measurements, the values were the averages based on the available data for that week. The averages were calculated as the sum of morning PEF values divided by the number of nonmissing assessments. ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 1 to 12

End point values	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID	FS MDPI 50/12.5 mcg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208	210	208	211
Units: liters/minute				
least squares mean (standard error)	12.3 (± 2.65)	28.9 (± 2.62)	26.3 (± 2.64)	32.0 (± 2.61)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Weekly Average of Total Daily (24 Hour) Use of Albuterol/Salbutamol Inhalation Aerosol (Number of Inhalations) Over Weeks 1 Through 12

End point title	Change From Baseline in the Weekly Average of Total Daily (24 Hour) Use of Albuterol/Salbutamol Inhalation Aerosol (Number of Inhalations) Over Weeks 1 Through 12
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End point description:

Participants recorded the number of inhalations of rescue medication (albuterol/salbutamol HFA MDI) each morning and evening in the electronic participant diary. An entry of 0 inhalations indicated no rescue medication was needed. To calculate the total daily use of albuterol/salbutamol inhalation aerosol (number of inhalations), the electronic participant diary entry on randomization visit (Baseline [Day 1]) was defined as the first day of analysis. The weekly average of the total daily inhalations was the average based on the available data for that week. The average was calculated as the sum of total daily inhalations over the 7 days for each analysis week divided by the number of nonmissing assessments. LS mean and standard error (SE) were obtained using mixed model for repeated measures (MMRM). ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 1 to 12

End point values	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID	FS MDPI 50/12.5 mcg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208	210	209	211
Units: inhalations				
least squares mean (standard error)	-0.2 (± 0.05)	-0.4 (± 0.05)	-0.5 (± 0.05)	-0.4 (± 0.05)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Weekly Average of the Total Daily Asthma Symptom Score Over Weeks 1 Through 12

End point title	Change From Baseline in the Weekly Average of the Total Daily Asthma Symptom Score Over Weeks 1 Through 12
End point description:	
Each participant assessed the asthma symptoms of cough, wheeze, shortness of breath, and chest tightness and entered a single score that was inclusive of all symptoms. Daytime Symptom Score (determined in the evening) ranged from 0=No symptoms to 5=Symptoms so severe that I could not go to work or perform normal daily activities. Nighttime Symptom Score (determined in the morning) ranged from 0=No symptoms to 4=Symptoms so severe that I did not sleep at all. Total daily asthma symptom score was average of daytime and nighttime scores. Total daily asthma symptom score ranged from 0 - 9 with 0=no symptoms and 9=severe symptoms. Weekly average was calculated as the sum of total daily asthma symptom scores over the 7 days for each analysis week divided by the number of nonmissing assessments. LS mean and SE were obtained using MMRM. ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Week 1 to 12	

End point values	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID	FS MDPI 50/12.5 mcg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208	210	209	211
Units: units on a scale				
least squares mean (standard error)	-0.1 (± 0.02)	-0.2 (± 0.02)	-0.2 (± 0.02)	-0.2 (± 0.02)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control (Measured by Childhood Asthma Control Test [C-ACT] Score) Over the 12 Week Treatment Period

End point title	Change From Baseline in Asthma Control (Measured by Childhood Asthma Control Test [C-ACT] Score) Over the 12 Week Treatment Period
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End point description:

C-ACT was a simple, participant-completed tool used for the assessment of overall asthma control. The first 4 items of the test were completed by the participant, while the last 3 items were completed by the participant's parents/legal guardians/caregivers. A total sum score based upon responses to all items was calculated to provide an overall measure of asthma control. The derived C-ACT score ranging from 0 to 27. These scores spanned the continuum of poor control of asthma (score ≤ 5) to complete control of asthma (score ≥ 25), with a cut off score of 19 indicating participants with poorly controlled asthma. LS mean and SE were obtained using MMRM. ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 1 to 12

End point values	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID	FS MDPI 50/12.5 mcg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	204	208	205	209
Units: units on a scale				
least squares mean (standard error)	4.5 (\pm 0.21)	5.1 (\pm 0.21)	5.5 (\pm 0.21)	5.4 (\pm 0.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Onset of Effect

End point title	Time to First Onset of Effect
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End point description:

The time to first onset of effect, defined as the first decrease from baseline in daily rescue medication use, was calculated based on the number of inhalations of rescue medication (albuterol/salbutamol hydrofluoroalkane metered-dose inhaler [HFA MDI] [90 mcg ex actuator] or equivalent) recorded by the participant each morning and evening in the participant diary built into the handheld device. ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint. Here, '99999' signifies data could not be calculated due to smaller number of participants with an event.

End point type	Secondary
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End point timeframe:

Baseline up to Week 12

End point values	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID	FS MDPI 50/12.5 mcg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208	210	208	211
Units: days				
median (confidence interval 95%)	20.0 (5.0 to 99999)	99999 (3.0 to 99999)	2.0 (2.0 to 2.0)	6.0 (2.0 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Discontinued From Investigational Medicinal Product (IMP) for Asthma Exacerbation During the 12 Week Treatment Period

End point title	Percentage of Participants who Discontinued From Investigational Medicinal Product (IMP) for Asthma Exacerbation During the 12 Week Treatment Period
End point description: ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' signifies participants evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Baseline up to Week 12	

End point values	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID	FS MDPI 50/12.5 mcg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	208	210	208	211
Units: percentage of participants				
number (not applicable)	6	2	1	2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 13

Adverse event reporting additional description:

Safety analysis set included all randomized participants who received at least 1 dose of IMP.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo MDPI
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Reporting group description:

Participants received matching placebo via MDPI for 12 weeks.

Reporting group title	Fp MDPI 25 mcg BID
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Reporting group description:

Participants received 1 inhalation of 25 mcg fluticasone propionate via MDPI BID (total daily dose: 50 mcg) for 12 weeks.

Reporting group title	Fp MDPI 50 mcg BID
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Reporting group description:

Participants received 1 inhalation of 50 mcg fluticasone propionate via MDPI BID (total daily dose: 100 mcg) for 12 weeks.

Reporting group title	FS MDPI 50/12.5 mcg BID
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Reporting group description:

Participants received 1 inhalation of 50/12.5 mcg fluticasone propionate/salmeterol via MDPI BID (total daily dose: 100/25 mcg) for 12 weeks.

Serious adverse events	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 209 (0.48%)	2 / 211 (0.95%)	1 / 208 (0.48%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	0 / 208 (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
Partial seizures			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	0 / 208 (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
Blood and lymphatic system disorders			

Lymphadenitis			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	0 / 208 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	0 / 208 (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 / 209 (0.48%)	1 / 211 (0.47%)	0 / 208 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Disruptive mood dysregulation disorder			
subjects affected / exposed	0 / 209 (0.00%)	0 / 211 (0.00%)	1 / 208 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 209 (0.00%)	1 / 211 (0.47%)	0 / 208 (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
Respiratory tract infection viral			
subjects affected / exposed	1 / 209 (0.48%)	0 / 211 (0.00%)	0 / 208 (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
Serious adverse events	FS MDPI 50/12.5 mcg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 211 (1.90%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Nervous system disorders			
Headache			
subjects affected / exposed	1 / 211 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	1 / 211 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 211 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 211 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 211 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Disruptive mood dysregulation disorder			
subjects affected / exposed	0 / 211 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 211 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory tract infection viral subjects affected / exposed	0 / 211 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo MDPI	Fp MDPI 25 mcg BID	Fp MDPI 50 mcg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 209 (5.26%)	8 / 211 (3.79%)	11 / 208 (5.29%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 209 (5.26%)	8 / 211 (3.79%)	11 / 208 (5.29%)
occurrences (all)	12	9	11

Non-serious adverse events	FS MDPI 50/12.5 mcg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 211 (4.27%)		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 211 (4.27%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2018	<p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none">• An unplanned blinded data quality evaluation and sample size reassessment was conducted. Based on the observed blinded 410 completed participants, the initial assumptions for SD and power calculation and the sample size were revised. Increase in number of participants enrolled.• Treatment compliance was assessed on both data from the dose counter and the diary.• "2-Dimensional tipping point" multiple imputation was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported