Clinical trial results:
A 26-Week Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate/Formoterol Fumarate Combination Formulation Compared With Mometasone Furoate and Formoterol Monotherapy in Subjects with Persistent Asthma Previously Treated With Medium-Dose Inhaled Glucocorticosteroids

Summary

EudraCT number	2006-001578-25
Trial protocol	HU EE DK
Global end of trial date	23 September 2008

Results information

Result version number	v1 (current)
This version publication date	05 April 2016
First version publication date	09 May 2015

Trial information

Trial identification

Sponsor protocol code	P04334

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00383240
WHO universal trial number (UTN)	-
Other trial identifiers	MK-0887A-092: Merck protocol number

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000025-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2008
Global end of trial reached?	Yes
Global end of trial date	23 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To determine the efficacy of mometasone furoate/formoterol (MF/F) metered-dose inhaler (MDI) 200/10 mcg twice each day (BID) compared with mometasone furoate (MF MDI 200 mcg BID), in order to assess the added benefit of formoterol (F MDI 10 mcg BID) to the combination.

2. To determine the efficiacy of MF/F MDI 200/10 mcg BID compared with F MDI 10 mcg BID, in order to assess the benefit of the steroid component of the combination.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measures defined for this individual study were in place for the protection of trial subjects: subjects were provided with locally purchased short-acting ß-agonist (SABA: albuterol MDI 90 mcg in the United States; salbutamol MDI 100 mcg outside of the United States) to treat asthma symptoms and were also provided with locally purchased oral prednisone/prednisolone for acute self-administration.

Background therapy:

Subjects were provided with locally purchased SABA (albuterol MDI 90 mcg in the United States; salbutamol MDI 100 mcg outside of the United States) to treat asthma symptoms and were also provided with locally purchased oral prednisone/prednisolone for acute self-administration.

Evidence for comparator: -

Actual start date of recruitment	28 September 2006
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	Denmark: 1
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Hungary: 86
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Costa Rica: 22
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Ecuador: 7

Country: Number of subjects enrolled	Guatemala: 17
Country: Number of subjects enrolled	India: 58
Country: Number of subjects enrolled	Mexico: 45
Country: Number of subjects enrolled	Philippines: 47
Country: Number of subjects enrolled	Poland: 113
Country: Number of subjects enrolled	Russian Federation: 41
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Ukraine: 53
Country: Number of subjects enrolled	United States: 264
Worldwide total number of subjects	781
EEA total number of subjects	211

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)	63
Adults (18-64 years)	677
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants screened for this study were 12 years of age or older, had a diagnosis of asthma of at least 12 months duration, were using a medium daily dose of inhaled coticosteroids (ICS) for at least 12 weeks and were on a stable ICS regimen for at least 2 weeks prior to Screening.

Period 1

Period 1 title	26-Week Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	MF/F MDI 200/10 mcg BID

Arm description:

Participants receive MF/F MDI 200/10 mcg BID for up to 26 weeks

Arm type	Experimental
Investigational medicinal product name	mometasone furoate/formoterol fumarate
Investigational medicinal product code	
Other name	MK-0887A, SCH 418131
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MF/F MDI 200/10 mcg BID for up to 26 weeks

Arm title	MF MDI 200 mcg BID

Arm description:

Participants receive MF MDI 200 mcg BID for up to 26 weeks

Arm type	Experimental
Investigational medicinal product name	mometasone furoate
Investigational medicinal product code	
Other name	MK-0887, SCH 032088
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MF MDI 200 mcg BID for up to 26 weeks

Arm title	F MDI 10 mcg BID

Arm description:

Participants receive F MDI 10 mcg BID for up to 26 weeks

Arm type	Experimental
Investigational medicinal product name	formoterol fumarate
Investigational medicinal product code	
Other name	Foradil®, MK-5571
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:
F MDI 10 mcg BID for up to 26 weeks

Arm title	Placebo MDI BID
Arm description:	
Participants receive placebo MDI BID for up to 26 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:
Placebo MDI BID for up to 26 weeks

Number of subjects in period 1	MF/F MDI 200/10 mcg BID	MF MDI 200 mcg BID	F MDI 10 mcg BID
Started	191	192	202
Treated	191	192	202
Completed	156	159	117
Not completed	35	33	85
Consent withdrawn by subject	6	4	11
Administrative	1	1	-
Adverse event, non-fatal	4	6	9
Non-compliance with protocol	4	5	9
Lost to follow-up	3	-	-
Lack of efficacy	8	13	47
Protocol deviation	9	4	9

Number of subjects in period 1	Placebo MDI BID
Started	196
Treated	195
Completed	119
Not completed	77
Consent withdrawn by subject	13
Administrative	-
Adverse event, non-fatal	7
Non-compliance with protocol	6
Lost to follow-up	2
Lack of efficacy	46

Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	MF/F MDI 200/10 mcg BID
Reporting group description:	
Participants receive MF/F MDI 200/10 mcg BID for up to 26 weeks	
Reporting group title	MF MDI 200 mcg BID
Reporting group description:	
Participants receive MF MDI 200 mcg BID for up to 26 weeks	
Reporting group title	F MDI 10 mcg BID
Reporting group description:	
Participants receive F MDI 10 mcg BID for up to 26 weeks	
Reporting group title	Placebo MDI BID
Reporting group description:	
Participants receive placebo MDI BID for up to 26 weeks	

Reporting group values	MF/F MDI 200/10 mcg BID	MF MDI 200 mcg BID	F MDI 10 mcg BID
Number of subjects	191	192	202
Age categorical Units: Subjects			
Adolescents (12-17 years)	19	10	18
Adults (18-64 years)	161	173	174
From 65-84 years	11	9	10
Age continuous Units: years			
arithmetic mean	42.9	42.8	41.9
standard deviation	± 16.3	± 14.9	± 15.3
Gender categorical Units: Subjects			
Female	97	112	129
Male	94	80	73

Reporting group values	Placebo MDI BID	Total	
Number of subjects	196	781	
Age categorical Units: Subjects			
Adolescents (12-17 years)	16	63	
Adults (18-64 years)	169	677	
From 65-84 years	11	41	
Age continuous Units: years			
arithmetic mean	41.9		
standard deviation	± 15.3	-	
Gender categorical Units: Subjects			
Female	122	460	
Male	74	321	

End points

End points reporting groups

Reporting group title	MF/F MDI 200/10 mcg BID
Reporting group description:	
Participants receive MF/F MDI 200/10 mcg BID for up to 26 weeks	
Reporting group title	MF MDI 200 mcg BID
Reporting group description:	
Participants receive MF MDI 200 mcg BID for up to 26 weeks	
Reporting group title	F MDI 10 mcg BID
Reporting group description:	
Participants receive F MDI 10 mcg BID for up to 26 weeks	
Reporting group title	Placebo MDI BID
Reporting group description:	
Participants receive placebo MDI BID for up to 26 weeks	

Primary: Mean Area Under the Time Curve From 0 to 12 Hours (AUC[0-12h]) of Change From Baseline to Week 12 in Forced Expiratory Volume in One Second (FEV1)

End point title	Mean Area Under the Time Curve From 0 to 12 Hours (AUC[0-12h]) of Change From Baseline to Week 12 in Forced Expiratory Volume in One Second (FEV1)
End point description:	
Baseline was the mean of two pre-dose FEV1 measurements on Day 1. Endpoint was the last post-Baseline non-missing FEV1 AUC(0-12h) result carried forward. Post-Baseline least squares (LS) means and pooled standard deviations were obtained from the analysis of covariance (ANCOVA) model with treatment, site effects and the Baseline FEV1 (liters) as a covariate.	
End point type	Primary
End point timeframe:	
Baseline and Week 12 End Point	

End point values	MF/F MDI 200/10 mcg BID	MF MDI 200 mcg BID	F MDI 10 mcg BID	Placebo MDI BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	190[1]	190[2]	202[3]	193[4]
Units: liters x hours				
least squares mean (standard deviation)	3.19 (± 3.98)	1.31 (± 3.98)	1.6 (± 3.98)	0.51 (± 3.98)

Notes:

[1] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[2] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[3] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[4] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

Statistical analyses

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID

Statistical analysis description: MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison P-value	
Comparison groups	MF/F MDI 200/10 mcg BID v MF MDI 200 mcg BID
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. Placebo MDI BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	MF/F MDI 200/10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDI 200 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF MDI 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.491
Method	ANCOVA

Statistical analysis title	MF MDI 200 mcg BID vs. Placebo MDI BID

Statistical analysis description:	
MF MDI 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v Placebo MDI BID
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	ANCOVA

Statistical analysis title	F MDI 10 mcg BID vs. Placebo MDI BID
Statistical analysis description:	
F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	F MDI 10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	ANCOVA

Primary: Number of Participants With At Least One Severe Asthma Exacerbation

End point title	Number of Participants With At Least One Severe Asthma Exacerbation

End point description:

A severe asthma exacerbation was defined as a clinically judged deterioration of asthma or a meaningful reduction in lung function based on any one of the following criteria during the Treatment Period: 1) A decrease in FEV1 (absolute value) below the Treatment Period stability limit at any visit during the Treatment Period. The Treatment Period stability limit was defined as 80% of the average of the two predose FEV1 measurements just prior to the first dose of randomized study medication. 2) A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment during the Treatment Period. The Treatment Period stability limit was defined as 70% of the respective mean AM or PM PEF obtained over the last 7 days immediately prior to receiving randomized study medication. 3) An occurrence of any clinical deterioration of asthma (i.e., asthma attack) that resulted in emergency treatment, hospitalization due to asthma or treatment with additional, excluded asthma medication.

End point type	Primary

End point timeframe:

26 weeks

End point values	MF/F MDI 200/10 mcg BID	MF MDI 200 mcg BID	F MDI 10 mcg BID	Placebo MDI BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	191[5]	192[6]	202[7]	196[8]
Units: participants	58	65	109	109

Notes:

[5] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[6] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[7] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.
[8] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

Statistical analyses

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v MF MDI 200 mcg BID
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.565
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. Placebo MDI BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDI 200 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF MDI 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v F MDI 10 mcg BID

Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDI 200 mcg BID vs. Placebo MDI BID
Statistical analysis description:	
MF MDI 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v Placebo MDI BID
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	F MDI 10 mcg BID vs. Placebo MDI BID
Statistical analysis description:	
F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	F MDI 10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.967
Method	ANCOVA

Secondary: Change from Baseline to Week 26 in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ[S]) Score

End point title	Change from Baseline to Week 26 in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ[S]) Score
End point description:	
The AQLQ(S) consists of 32 questions covering 4 domains: symptoms, emotional functioning, impact of environmental stimuli and activity limitation. Responses to each question were to reflect participant experience over the previous 2 weeks and were scaled from 1 (worst case) to 7 (best case). End point was the last post-Baseline non-missing AQLQ(S) result carried forward. Post-Baseline LS means and pooled standard deviations were obtained from the ANCOVA model with treatment, site effects and the Baseline AQLQ(S) score as a covariate.	
End point type	Secondary
End point timeframe:	
Baseline and Week 26 End Point	

End point values	MF/F MDI 200/10 mcg BID	MF MDI 200 mcg BID	F MDI 10 mcg BID	Placebo MDI BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	183[9]	189[10]	187[11]	189[12]
Units: score on a scale				
least squares mean (standard deviation)	0.49 (± 0.85)	0.37 (± 0.85)	0.05 (± 0.85)	-0.01 (± 0.85)

Notes:

[9] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[10] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[11] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[12] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

Statistical analyses

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwiase comparison p-value	
Comparison groups	MF MDI 200 mcg BID v MF/F MDI 200/10 mcg BID
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwiase comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. Placebo MDI BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwiase comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDI 200 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF MDI 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDI 200 mcg BID vs. Placebo MDI BID
Statistical analysis description: MF MDI 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v Placebo MDI BID
Number of subjects included in analysis	378
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	F MDI 10 mcg BID vs. Placebo MDI BID
Statistical analysis description: F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	F MDI 10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.521
Method	ANCOVA

Secondary: Change from Baseline to Week 26 in Asthma Control Questionnaire (ACQ) Score

End point title	Change from Baseline to Week 26 in Asthma Control Questionnaire (ACQ) Score

End point description:

The ACQ consists of 7 questions covering awakenings due to asthma, symptoms when awoken, activity limitations, shortness of breath, wheezing, number of puffs of SABA used and FEV1 % predicted. Responses to questions were to reflect participant experience over the previous week and were each scaled from 0 (best case) to 6 (worst case). End point was the last post-Baseline non-missing ACQ result carried forward. Post-Baseline LS means and pooled standard deviations were obtaines from the ANCOVA model with treatment, site effects and the Baseline ACQ score as a covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 26 End Point

End point values	MF/F MDI 200/10 mcg BID	MF MDI 200 mcg BID	F MDI 10 mcg BID	Placebo MDI BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	179[13]	186[14]	184[15]	187[16]
Units: score on a scale				
least squares mean (standard deviation)	-0.4 (± 0.74)	-0.23 (± 0.74)	0.11 (± 0.74)	0.14 (± 0.74)

Notes:

[13] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[14] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[15] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[16] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

Statistical analyses

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v MF MDI 200 mcg BID
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. Placebo MDI BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v Placebo MDI BID

Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDI 200 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF MDI 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDI 200 mcg BID vs. Placebo MDI BID
Statistical analysis description: MF MDI 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v Placebo MDI BID
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	F MDI 10 mcg BID vs. Placebo MDI BID
Statistical analysis description: F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	F MDI 10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.738
Method	ANCOVA

Secondary: Change from Baseline Across the Treatment Period in Percentage of Nights With Nocturnal Awakenings Due to Asthma that Require Use of SABA

End point title	Change from Baseline Across the Treatment Period in Percentage of Nights With Nocturnal Awakenings Due to Asthma that Require Use of SABA

End point description:

Baseline percentage of nights with nocturnal awakenings that required use of SABA included data from the last week before first dose of randomized study drug. End point percentage included data from the entire 26-week Treatment Period. Post-Baseline LS means and pooled standard deviations were obtained from the ANCOVA model with treatment, site effects and the Baseline percentage as a covariate.

End point type	Secondary

End point timeframe:

Baseline and 26-week Treatment Period End Point

End point values	MF/F MDI 200/10 mcg BID	MF MDI 200 mcg BID	F MDI 10 mcg BID	Placebo MDI BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	186[17]	191[18]	199[19]	194[20]
Units: percentage of nocturnal awakenings				
least squares mean (standard deviation)	-0.08 (± 0.17)	-0.05 (± 0.17)	0.01 (± 0.17)	0 (± 0.17)

Notes:

[17] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[18] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[19] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[20] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

Statistical analyses

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID

Statistical analysis description:

MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison p-value

Comparison groups	MF/F MDI 200/10 mcg BID v MF MDI 200 mcg BID
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID

Statistical analysis description:

MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison p-value

Comparison groups	MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF/F MDI 200/10 mcg BID vs. Placebo MDI BID
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDi 200 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description: MF MDi 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v F MDI 10 mcg BID
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	MF MDi 200 mcg BID vs. Placebo MDI BID
Statistical analysis description: MF MDi 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	MF MDI 200 mcg BID v Placebo MDI BID
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA

Statistical analysis title	F MDI 10 mcg BID vs. Placebo MDI BID
Statistical analysis description: F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value	
Comparison groups	F MDI 10 mcg BID v Placebo MDI BID
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.601
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 26 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	MF/F MDI 200/10 mcg BID
Reporting group description: Participants receive MF/F MDI 200/10 mcg BID for up to 26 weeks	
Reporting group title	Placebo MDI BID
Reporting group description: Participants receive placebo MDI BID for up to 26 weeks	
Reporting group title	F MDI 10 mcg BID
Reporting group description: Participants receive F MDI 10 mcg BID for up to 26 weeks	
Reporting group title	MF MDI 200 mcg BID
Reporting group description: Participants receive MF MDI 200 mcg BID for up to 26 weeks	

Serious adverse events	MF/F MDI 200/10 mcg BID	Placebo MDI BID	F MDI 10 mcg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 191 (2.62%)	3 / 196 (1.53%)	3 / 202 (1.49%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyosarcoma			
subjects affected / exposed	1 / 191 (0.52%)	0 / 196 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Malignant Melanoma			
subjects affected / exposed	0 / 191 (0.00%)	0 / 196 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus Fracture			

subjects affected / exposed	0 / 191 (0.00%)	1 / 196 (0.51%)	0 / 202 (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
Surgical and medical procedures			
Spinal Decompression			
subjects affected / exposed	0 / 191 (0.00%)	1 / 196 (0.51%)	0 / 202 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 191 (0.52%)	0 / 196 (0.00%)	0 / 202 (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
Hypoaesthesia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 196 (0.00%)	0 / 202 (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
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 196 (0.00%)	0 / 202 (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
Vaginal Haemorrhage			
subjects affected / exposed	1 / 191 (0.52%)	0 / 196 (0.00%)	0 / 202 (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 / 191 (0.00%)	0 / 196 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis Atopic			

subjects affected / exposed	0 / 191 (0.00%)	1 / 196 (0.51%)	0 / 202 (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
Eczema			
subjects affected / exposed	1 / 191 (0.52%)	0 / 196 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 196 (0.00%)	0 / 202 (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
Viral Infection			
subjects affected / exposed	1 / 191 (0.52%)	0 / 196 (0.00%)	0 / 202 (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
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 196 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MF MDI 200 mcg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 192 (1.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyosarcoma			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant Melanoma			

subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Humerus Fracture			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Spinal Decompression			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal Haemorrhage			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis Atopic			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eczema			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 192 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral Infection			
subjects affected / exposed	0 / 192 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 192 (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	MF/F MDI 200/10 mcg BID	Placebo MDI BID	F MDI 10 mcg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 191 (16.23%)	30 / 196 (15.31%)	29 / 202 (14.36%)
Nervous system disorders			

Headache			
subjects affected / exposed	9 / 191 (4.71%)	7 / 196 (3.57%)	6 / 202 (2.97%)
occurrences (all)	10	10	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 191 (6.28%)	7 / 196 (3.57%)	13 / 202 (6.44%)
occurrences (all)	13	8	14
Upper respiratory tract infection			
subjects affected / exposed	11 / 191 (5.76%)	17 / 196 (8.67%)	12 / 202 (5.94%)
occurrences (all)	13	17	16

Non-serious adverse events	MF MDI 200 mcg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 192 (18.23%)		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 192 (5.21%)		
occurrences (all)	17		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 192 (7.81%)		
occurrences (all)	22		
Upper respiratory tract infection			
subjects affected / exposed	16 / 192 (8.33%)		
occurrences (all)	16		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2007	Amendment 01: The main reasons for Amendment 01 were 1) to clarify that open-label run-in medication was to be dispensed at Visit 1, but that participants were NOT to start taking open-label MF MDI (run-in medication) until after the laboratory results were available and found to be clinically acceptable, 2) to clarify inclusion and exclusion criteria and 3) to modify the age of participants for countries such as Russia where minors are not permitted in clinical studies and therefore only adults (participants ≥18 years of age) so as to reflect various Ethics Committees and Competent Authorities requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported