

**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 Low-Dose Inhaled Glucocorticosteroids****Summary**

EudraCT number	2006-001577-13
Trial protocol	HU EE DK
Global end of trial date	31 August 2008

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	05 July 2015

Trial information**Trial identification**

Sponsor protocol code	P04073
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00383552
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-0887A-081

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 Sharpe & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharpe & 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	31 August 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2008
Global end of trial reached?	Yes
Global end of trial date	31 August 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel-group study, evaluating the efficacy of mometasone furoate/formoterol fumarate (MF/F) metered dose inhaler (MDI) versus MF for 26 weeks. Prior to the 26-week double-blind Treatment Period, participants will receive open-label (OL) MF MDI 100 mcg twice daily (BID) for 2 to 3 weeks during the Run-in Period. Efficacy will be measured by the Area Under the Curve from 0 to 12 hours (AUC[0-12 hrs]) of the change from Baseline to the Week 12 Endpoint in Forced Expiratory Volume in One Second (FEV1) and by the time-to-first severe asthma exacerbation across the 26-week treatment period. The primary hypothesis is that MF/F 100/10 mcg BID is significantly more effective than MF 100 mcg BID with respect to change from baseline to week 12 in FEV(0-12 hr) AUC and significantly more effective than F 10 mcg BID in the time-to-first asthma exacerbation over a 26-week treatment period.

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:

All participants in the current study were carefully monitored for asthma exacerbations and were provided with an asthma action plan with immediate availability of emergency rescue oral steroids (e.g. prednisone) and short-acting beta 2-agonists (SABA), and had access to around-the-clock physician contact. Participants were provided with a SABA Metered Dose Inhaler (MDI) at the Screening Visit for use as rescue medication during the study, and were advised not to take the SABA via an MDI or a nebulizer regularly or in anticipation of asthma symptoms. Rescue medication was recorded in the Patient Diary.

Background therapy: -

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	Bulgaria: 108
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Croatia: 29

Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Guatemala: 7
Country: Number of subjects enrolled	Hungary: 64
Country: Number of subjects enrolled	India: 67
Country: Number of subjects enrolled	Mexico: 36
Country: Number of subjects enrolled	Philippines: 35
Country: Number of subjects enrolled	Poland: 106
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Ukraine: 33
Country: Number of subjects enrolled	United States: 356
Worldwide total number of subjects	882
EEA total number of subjects	315

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)	139
Adults (18-64 years)	684
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

882 participants enrolled in the open-label Run-In Period, of which 746 participants were randomized into 1 of 4 arms. Of 746 randomized participants, 536 participants overall completed the Treatment Period, with 210 participants overall discontinued investigational treatment early. All randomized participants received ≥ 1 dose of study medication.

Period 1

Period 1 title	Open-Label Run-In Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	OL MF MDI 100 MCG BID
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Arm description:

Participants received 2 to 3 weeks (approximately) of open-label, run-in medication with MF MDI 100 mcg BID prior to the 26-week double-blind treatment period.

Arm type	Run-in
Investigational medicinal product name	Mometasone furoate MDI (MF MDI)
Investigational medicinal product code	
Other name	MK-0887, SCH 032088
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Open-label MF 100 mcg via metered dose inhaler twice daily for approximately 2 to 3 weeks.

Number of subjects in period 1	OL MF MDI 100 MCG BID
Started	882
Completed	746
Not completed	136
Did not meet protocol eligibility	84
Administrative	2
Adverse event, non-fatal	6
Subject did not wish to continue, reason related	1
Treatment Failure	2
Subject did not wish to continue, reason unrelated	20
Non-compliance with protocol	12
Lost to follow-up	9

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MF/F MDI 100/10 mcg BID

Arm description:

Participants received mometasone furoate 100 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Mometasone furoate 100 mcg/formoterol 10 mcg (MF/F) combination
Investigational medicinal product code	
Other name	MK-0887A, SCH 418131
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

MF/F 100/10 mcg via a metered dose inhaler (MDI) twice daily for 26 weeks

Arm title	MF MDI 100 mcg BID
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Arm description:

Participants received mometasone furoate 100 mcg taken twice daily for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Mometasone furoate MDI (MF MDI)
Investigational medicinal product code	
Other name	SCH 032088
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

MF 100 mcg via metered dose inhaler twice daily for 26 weeks

Arm title	F MDI 10 mcg BID
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Arm description:

Participants received formoterol fumarate (F) 10 mcg taken twice daily for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Formoterol fumarate (F)
Investigational medicinal product code	
Other name	Foradil®, MK-5571
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

F 10 mcg via a metered dose inhaler (MDI) twice daily for 26 weeks

Arm title	Placebo BID
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Arm description:

Participants received placebo taken twice daily for 26 weeks.

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

Dosage and administration details:

Placebo twice daily for 26 weeks

Notes:

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

Justification: Period 1 represents an open-label run-in to standardize treatment - not all of these subjects participated in the trial.

Period 2 (baseline period) represents the randomized double-blind treatment phase. This is the primary study period of interest, thus baseline characteristics are reported for this period.

Number of subjects in period 2^[2]	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID
Started	182	188	188
Completed	146	147	127
Not completed	36	41	61
Did not meet protocol eligibility	8	6	2
Did not wish to continue (unrelated)	4	9	5
Administrative	1	-	1
Adverse event, non-fatal	7	6	9
Did not wish to continue (related)	1	-	2
Non-compliance with protocol	11	6	8
Lost to follow-up	-	1	5
Lack of efficacy	4	13	29

Number of subjects in period 2^[2]	Placebo BID
Started	188
Completed	116
Not completed	72
Did not meet protocol eligibility	3
Did not wish to continue (unrelated)	6
Administrative	1
Adverse event, non-fatal	6
Did not wish to continue (related)	3
Non-compliance with protocol	10
Lost to follow-up	1
Lack of efficacy	42

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 in the baseline period represent those who were randomized to treatment on study; this is the primary population of interest. The worldwide number represents all enrolled subjects who entered an open-label run-in to standardize treatment - not all of these subjects participated in trial.

Baseline characteristics

Reporting groups

Reporting group title	MF/F MDI 100/10 mcg BID
Reporting group description:	Participants received mometasone furoate 100 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 26 weeks.
Reporting group title	MF MDI 100 mcg BID
Reporting group description:	Participants received mometasone furoate 100 mcg taken twice daily for 26 weeks.
Reporting group title	F MDI 10 mcg BID
Reporting group description:	Participants received formoterol fumarate (F) 10 mcg taken twice daily for 26 weeks.
Reporting group title	Placebo BID
Reporting group description:	Participants received placebo taken twice daily for 26 weeks.

Reporting group values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID
Number of subjects	182	188	188
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	37.1 ± 16.9	39.4 ± 16.7	38.5 ± 15.6
Gender categorical Units: Subjects			
Female	99	105	103
Male	83	83	85

Reporting group values	Placebo BID	Total	
Number of subjects	188	746	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	38.1 ± 17.4	-	
Gender categorical Units: Subjects			
Female	106	413	
Male	82	333	

End points

End points reporting groups

Reporting group title	OL MF MDI 100 MCG BID
Reporting group description: Participants received 2 to 3 weeks (approximately) of open-label, run-in medication with MF MDI 100 mcg BID prior to the 26-week double-blind treatment period.	
Reporting group title	MF/F MDI 100/10 mcg BID
Reporting group description: Participants received mometasone furoate 100 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 26 weeks.	
Reporting group title	MF MDI 100 mcg BID
Reporting group description: Participants received mometasone furoate 100 mcg taken twice daily for 26 weeks.	
Reporting group title	F MDI 10 mcg BID
Reporting group description: Participants received formoterol fumarate (F) 10 mcg taken twice daily for 26 weeks.	
Reporting group title	Placebo BID
Reporting group description: Participants received placebo taken twice daily for 26 weeks.	

Primary: Mean area under the time curve from 0 to 12 hours (AUC [0-12 hours]) of change from Baseline to Week 12 in forced expiratory volume (liters) in 1 second (FEV1)

End point title	Mean area under the time curve from 0 to 12 hours (AUC [0-12 hours]) of change from Baseline to Week 12 in forced expiratory volume (liters) in 1 second (FEV1)
End point description: The average of the two predose FEV1 measurements (30 minutes prior to dosing and 0 hour, immediately prior to dosing) at the Baseline Visit were subtracted from each of the serial measurements over the 12-hour period. The AUC was calculated based on these changes from Baseline evaluations. The comparison was for MF/F vs MF. Standard deviation was pooled.	
End point type	Primary
End point timeframe: Baseline to Week 12	

End point values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	155	156	146	129
Units: liters x hours				
least squares mean (standard deviation)	4 (± 3.71)	2.53 (± 3.71)	3.83 (± 3.71)	1.11 (± 3.71)

Statistical analyses

Statistical analysis title	MF/F MDI 100/10 mcg BID vs. MF MDI 100 mcg BID
Statistical analysis description:	
Least Squares (LS) Means and pooled standard deviations (Pstd) for post-baseline evaluations were obtained from the ANCOVA model with treatment, site effects, and the baseline FEV1 (liters) as a covariate. BL was the mean of two pre-dose measurements (30 minutes before dosing and 0 hour, immediately before dosing) on Day 1. The last post-BL non-missing FEV1 AUC(0-12 hr) result carried forward was used.	
Comparison groups	MF/F MDI 100/10 mcg BID v MF MDI 100 mcg BID
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA

Primary: Median Time-to-first severe asthma exacerbation over the 26-week Treatment Period

End point title	Median Time-to-first severe asthma exacerbation over the 26-week Treatment Period ^[1]
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End point description:

Severe asthma exacerbation refers to an occurrence of a decrease below 80% of Baseline in FEV1, a decrease below 70% of Baseline in peak expiratory flow (PEF) on 2 consecutive days or a clinical deterioration of asthma resulting in emergency treatment, hospitalization or treatment with asthma medication. Medians for time-to-event outcomes are estimated for those who had events.

End point type	Primary
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End point timeframe:

Across the 26 week treatment period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were performed on this endpoint.

End point values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[2]	53 ^[3]	84 ^[4]	86 ^[5]
Units: days				
median (inter-quartile range (Q1-Q3))	45.5 (11 to 101)	54 (12 to 98)	51.5 (16.5 to 125.5)	27.5 (8 to 87)

Notes:

[2] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[3] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[4] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[5] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with at least one severe asthma exacerbation at week 26

End point title	Number of Participants with at least one severe asthma exacerbation at week 26
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End point description:

Severe asthma exacerbation refers to an occurrence of a decrease below 80% of Baseline in FEV1, a decrease below 70% of Baseline in PEF on 2 consecutive days and or a clinical deterioration of asthma resulting in emergency treatment, hospitalization or treatment with asthma medication.

End point type Primary

End point timeframe:

Week 26

End point values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	182 ^[6]	188 ^[7]	188 ^[8]	188 ^[9]
Units: Participants				
number (not applicable)	30	53	84	86

Notes:

[6] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[7] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[8] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[9] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

Statistical analyses

Statistical analysis title MF/F MDI 100/10 mcg BID vs. F MDI 10 mcg BID

Statistical analysis description:

MF/F MDI 100/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value

Comparison groups MF/F MDI 100/10 mcg BID v F MDI 10 mcg BID

Number of subjects included in analysis 370

Analysis specification Pre-specified

Analysis type superiority

P-value = 0.006

Method Logrank

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

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

End point description:

ACQ consists of seven questions each scaled from 0 (best case) to 6 (worst case). The comparison was for MF/F vs placebo. Standard deviation was pooled.

End point type Secondary

End point timeframe:

Baseline to Week 26

End point values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	143 ^[10]	145 ^[11]	129 ^[12]	116 ^[13]
Units: units on a scale				
least squares mean (standard deviation)				
Baseline	1.34 (± 0.71)	1.29 (± 0.6)	1.38 (± 0.76)	1.23 (± 0.71)
Change from Baseline	-0.4 (± 0.65)	-0.32 (± 0.65)	-0.12 (± 0.65)	-0.11 (± 0.65)

Notes:

[10] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[11] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[12] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[13] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

Statistical analyses

Statistical analysis title	MF/F MDI 100/10 mcg BID vs. Placebo BID
Statistical analysis description:	
Post-Baseline LS Means and Pstd (pooled standard deviations) were obtained from the ANCOVA model with treatment (trt), site effects, and the Baseline (Base) as a covariate. Baseline LS Means excluded the covariate. The last post-BL non-missing ACQ result carried forward was used.	
Comparison groups	MF/F MDI 100/10 mcg BID v Placebo BID
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA

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

End point title	Change from Baseline to Week 26 in Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) Total Score
End point description:	
AQLQ(S) consists of 32 questions each scaled from 1 (worst case) to 7 (best case). The comparison was for MF/F vs placebo. Standard deviation was pooled.	
End point type	Secondary
End point timeframe:	
Baseline to Week 26	

End point values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	144 ^[14]	147 ^[15]	129 ^[16]	117 ^[17]
Units: units on a scale				
least squares mean (standard deviation)				
Baseline	5.6 (± 0.93)	5.65 (± 1)	5.6 (± 0.98)	5.76 (± 1.02)

Change from Baseline	0.44 (± 0.73)	0.39 (± 0.73)	0.15 (± 0.73)	0.06 (± 0.73)
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Notes:

[14] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[15] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[16] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[17] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

Statistical analyses

Statistical analysis title	MF/F MDI 100/10 mcg BID vs. Placebo BID
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Statistical analysis description:

Post-Baseline LS Means and Pstd (pooled standard deviations) are obtained from the ANCOVA model with treatment, site effects and the baseline as a covariate. The last post-Baseline non-missing AQLQ result carried forward.

Comparison groups	MF/F MDI 100/10 mcg BID v Placebo BID
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Change from Baseline in proportion of nights across the treatment period with nocturnal awakenings due to asthma which require use of short-acting beta agonists (SABA)

End point title	Change from Baseline in proportion of nights across the treatment period with nocturnal awakenings due to asthma which require use of short-acting beta agonists (SABA)
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End point description:

Baseline is the proportion of nights of the last week (Days -7 to 1) prior to first dose with nocturnal awakenings. Scale is measured as 0 to 1 with 0=no awakenings to 1=awakenings every night. The comparison was for MF/F vs placebo. Standard deviation was pooled.

End point type	Secondary
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End point timeframe:

Baseline to Endpoint

End point values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	181 ^[18]	185 ^[19]	185 ^[20]	188 ^[21]
Units: Proportion of Nights				
least squares mean (standard deviation)				
Baseline	0.13 (± 0.12)	0.12 (± 0.12)	0.15 (± 0.15)	0.13 (± 0.14)
Change from Baseline	-0.06 (± 0.16)	-0.03 (± 0.16)	-0.03 (± 0.16)	0.02 (± 0.16)

Notes:

[18] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[19] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[20] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

Statistical analyses

Statistical analysis title	MF/F MDI 100/10 mcg BID vs. Placebo BID
Statistical analysis description:	
Post-Baseline LS Means and Pstd (pooled standard deviations) were obtained from the ANCOVA model with treatment (Trt), site effects, and the Baseline (Base) as a covariate. Baseline LS Means excluded the covariate.	
Comparison groups	MF/F MDI 100/10 mcg BID v Placebo BID
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Change from Baseline in AM FEV1 pre-dose assessment, or trough FEV1, at Week 12

End point title	Change from Baseline in AM FEV1 pre-dose assessment, or trough FEV1, at Week 12
End point description:	
Trough FEV1 is a measure of the end-of-dosing interval. The comparison was for MF/F vs F. Standard deviation was pooled.	
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	160 ^[22]	163 ^[23]	160 ^[24]	137 ^[25]
Units: liters				
least squares mean (standard deviation)				
Baseline	2.5 (± 2.56)	2.41 (± 2.46)	2.47 (± 2.52)	2.46 (± 2.5)
Change from Baseline	0.18 (± 0.21)	0.16 (± 0.21)	0.11 (± 0.21)	0.04 (± 0.21)

Notes:

[22] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[23] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[24] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[25] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

Statistical analyses

Statistical analysis title	MF/F MDI 100/10 mcg BID vs. F MDI 10 mcg BID
Statistical analysis description:	
Post-Baseline LS Means and Model Effects were obtained from a longitudinal model with treatment (Trt), participant, visit, and visit-by-treatment as fixed effects, Baseline (Base) as a covariate, and random intercept. Screening/Baseline LS Means were obtained from an ANOVA model with treatment and site fixed effects.	
Comparison groups	F MDI 10 mcg BID v MF/F MDI 100/10 mcg BID
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073
Method	Longitudinal Model

Secondary: AUC(0-12 hour) of the change from Baseline to Week 12 in FEV1 for each body mass index (BMI) subgroup

End point title	AUC(0-12 hour) of the change from Baseline to Week 12 in FEV1 for each body mass index (BMI) subgroup
End point description:	
The average of the two predose FEV1 measurements (30 minutes prior to dosing and 0 hour, immediately prior to dosing) at the Baseline Visit were subtracted from each of the serial measurements over the 12-hour period. The AUC was calculated based on these changes from Baseline evaluations. BMI is a number calculated from a person's weight and height. The higher the number, the higher the amount of fat. The comparison was for MF/F vs placebo. Standard deviation was pooled.	
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	MF/F MDI 100/10 mcg BID	MF MDI 100 mcg BID	F MDI 10 mcg BID	Placebo BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	155 ^[26]	156 ^[27]	146 ^[28]	128 ^[29]
Units: Liter x hour				
least squares mean (standard deviation)				
Less than 25	5.24 (± 4.42)	3.19 (± 4.42)	4.34 (± 4.42)	2.22 (± 4.42)
25 to less than 30	3.36 (± 4.14)	3.23 (± 4.14)	4.26 (± 4.14)	1.22 (± 4.14)
30 or more	3.35 (± 3.68)	1.69 (± 3.68)	3.13 (± 3.68)	-0.73 (± 3.68)

Notes:

[26] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[27] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[28] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

[29] - All Randomized Participants with BL and any post-BL data (intent-to-treat principle).

Statistical analyses

Statistical analysis title	MF/F MDI 100/10 mcg BID v. Placebo BID
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Statistical analysis description:

Least Squares (LS) Means and Pstd for post-baseline evaluations were obtained from the ANCOVA model with treatment, site effects, and the baseline FEV1 (liters) as a covariate. BL was the mean of two pre-dose measurements (30 minutes before dosing and 0 hour, immediately before dosing) on Day 1. The

last post-BL non-missing FEV1 AUC(0-12 hr) result carried forward was used.

Comparison groups	MF/F MDI 100/10 mcg BID v Placebo BID
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 ^[30]
Method	ANCOVA

Notes:

[30] - BMI 25 to less than 30

Statistical analysis title	MF/F MDI 100/10 mcg BID vs. Placebo BID
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Statistical analysis description:

Least Squares (LS) Means and Pstd for post-baseline evaluations were obtained from the ANCOVA model with treatment, site effects, and the baseline FEV1 (liters) as a covariate. BL was the mean of two pre-dose measurements (30 minutes before dosing and 0 hour, immediately before dosing) on Day 1. The last post-BL non-missing FEV1 AUC(0-12 hr) result carried forward was used.

Comparison groups	MF/F MDI 100/10 mcg BID v Placebo BID
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[31]
Method	ANCOVA

Notes:

[31] - BMI less than 25

Statistical analysis title	MF/F MDI 100/10 mcg BID vs. Placebo BID
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Statistical analysis description:

Least Squares (LS) Means and Pstd for post-baseline evaluations were obtained from the ANCOVA model with treatment, site effects, and the baseline FEV1 (liters) as a covariate. BL was the mean of two pre-dose measurements (30 minutes before dosing and 0 hour, immediately before dosing) on Day 1. The last post-BL non-missing FEV1 AUC(0-12 hr) result carried forward was used.

Comparison groups	MF/F MDI 100/10 mcg BID v Placebo BID
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[32]
Method	ANCOVA

Notes:

[32] - BMI greater than or equal to 30

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Open Label Run-In + DB Treatment Period (Day -21 to Week 26)

Adverse event reporting additional description:

All participants treated with OL MF MDI and/or double-blind study medication are included in the safety population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	OL MF MDI 100 MCG BID
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Reporting group description:

Participants received 2 to 3 weeks (approximately) of open-label, run-in medication with MF MDI 100 mcg BID prior to the 26-week double-blind treatment period.

Reporting group title	MF/F MDI 100/10 MCG BID
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Reporting group description:

Participants received mometasone furoate 100 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 26 weeks.

Reporting group title	MF MDI 100 MCG BID
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Reporting group description:

Participants received mometasone furoate 100 mcg taken twice daily for 26 weeks.

Reporting group title	F MDI 10 MCG BID'
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Reporting group description:

Participants received formoterol fumarate (F) 10 mcg taken twice daily for 26 weeks.

Reporting group title	PLACEBO
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Reporting group description:

Participants received placebo taken twice daily for 26 weeks.

Serious adverse events	OL MF MDI 100 MCG BID	MF/F MDI 100/10 MCG BID	MF MDI 100 MCG BID
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 882 (0.23%)	4 / 182 (2.20%)	5 / 188 (2.66%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			
subjects affected / exposed	0 / 882 (0.00%)	1 / 182 (0.55%)	0 / 188 (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
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 882 (0.00%)	0 / 182 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pulmonary Valve Stenosis			
subjects affected / exposed	0 / 882 (0.00%)	1 / 182 (0.55%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 882 (0.00%)	0 / 182 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 882 (0.00%)	0 / 182 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal Ulcer			
subjects affected / exposed	0 / 882 (0.00%)	0 / 182 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysfunctional Uterine Bleeding			
subjects affected / exposed	0 / 882 (0.00%)	1 / 182 (0.55%)	0 / 188 (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
Fallopian Tube Cyst			
subjects affected / exposed	1 / 882 (0.11%)	0 / 182 (0.00%)	0 / 188 (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	1 / 882 (0.11%)	0 / 182 (0.00%)	0 / 188 (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
Pneumothorax			
subjects affected / exposed	0 / 882 (0.00%)	1 / 182 (0.55%)	0 / 188 (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
Pulmonary Embolism			
subjects affected / exposed	0 / 882 (0.00%)	0 / 182 (0.00%)	0 / 188 (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
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 882 (0.00%)	0 / 182 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 882 (0.00%)	1 / 182 (0.55%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 882 (0.00%)	0 / 182 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Pericarditis			
subjects affected / exposed	0 / 882 (0.00%)	0 / 182 (0.00%)	1 / 188 (0.53%)
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	F MDI 10 MCG BID'	PLACEBO	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pulmonary Valve Stenosis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal Ulcer			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Dysfunctional Uterine Bleeding			

subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fallopian Tube Cyst			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (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 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Pericarditis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	OL MF MDI 100 MCG BID	MF/F MDI 100/10 MCG BID	MF MDI 100 MCG BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 882 (2.49%)	33 / 182 (18.13%)	37 / 188 (19.68%)
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 882 (1.70%)	12 / 182 (6.59%)	11 / 188 (5.85%)
occurrences (all)	18	17	18
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 882 (0.34%)	17 / 182 (9.34%)	13 / 188 (6.91%)
occurrences (all)	3	19	15
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 882 (0.57%)	10 / 182 (5.49%)	17 / 188 (9.04%)
occurrences (all)	5	11	19

Non-serious adverse events	F MDI 10 MCG BID'	PLACEBO	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 188 (17.02%)	24 / 188 (12.77%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 188 (4.79%)	7 / 188 (3.72%)	
occurrences (all)	9	10	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 188 (3.72%)	5 / 188 (2.66%)	
occurrences (all)	7	5	
Upper Respiratory Tract Infection			

subjects affected / exposed	20 / 188 (10.64%)	12 / 188 (6.38%)	
occurrences (all)	26	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported