Clinical trial results:
A 12-Week Efficacy and Safety Study of Two Doses of Mometasone Furoate/Formoterol Combination Formulation Compared With Mometasone Furoate Monotherapy, in Persistent Asthmatics Previously treated With High-Dose Inhaled Glucocorticosteroids

Summary

EudraCT number	2005-005910-20
Trial protocol	HU DK
Global end of trial date	30 January 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	P04431

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00381485
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-0887A-099

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	30 January 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2008
Global end of trial reached?	Yes
Global end of trial date	30 January 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, multicenter, double blind, parallel-group study evaluating the efficacy of mometasone furoate/formoterol fumarate (MF/F) metered dose inhaler (MDI) 400/10 mcg twice daily (BID) compared with MF MDI 400 mcg BID for 12 weeks. Prior to the 12-week double-blind treatment period, participants will receive open-label MF MDI 400 mcg BID for 2 to 3 weeks during the open-label (OL) run-in period. Efficacy will be measured by the area under the time curve from 0 to 12 hours (AUC [0-12 hr]) of the change from Baseline (BL) to the Week 12 Endpoint in forced expiratory volume in one second (FEV1).

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	17 July 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: 2
Country: Number of subjects enrolled	Hungary: 107
Country: Number of subjects enrolled	Argentina: 28
Country: Number of subjects enrolled	Bulgaria: 79
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Chile: 23
Country: Number of subjects enrolled	Colombia: 24
Country: Number of subjects enrolled	Guatemala: 31

Country: Number of subjects enrolled	Peru: 24
Country: Number of subjects enrolled	Poland: 129
Country: Number of subjects enrolled	Russian Federation: 158
Country: Number of subjects enrolled	Ukraine: 132
Country: Number of subjects enrolled	United States: 93
Worldwide total number of subjects	834
EEA total number of subjects	317

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)	66
Adults (18-64 years)	664
From 65 to 84 years	104
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

834 participants enrolled in the open-label Run-In Period, of which 728 participants were randomized into 1 of 3 arms. Of 728 randomized participants, 643 participants overall completed the Treatment Period, while 85 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 400 MCG BID

Arm description:

Participants received 2 to 3 weeks (approximately) of open-label, run-in medication with MF MDI 400 mcg BID prior to the 12-week double-blind treatment period.

Arm type	Run-In
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:

Open-label MF 400 mcg via metered dose inhaler twice daily for approximately 2 to 3 weeks.

Number of subjects in period 1	OL MF MDI 400 MCG BID
Started	834
Completed	728
Not completed	106
Did not meet protocol eligibility	76
Adverse event, non-fatal	9
Treatment Failure	1
Subject did not wish to continue-reasons related	16
Subject did not wish to continue-reasons unrelated	1
Lost to follow-up	3

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 200/10 mcg BID

Arm description:

Participants received mometasone Furoate 200 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Mometasone furoate 200 mcg/formoterol 10 mcg (MF/F) combination
Investigational medicinal product code	
Other name	SCH 418131
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

MF/F 200/10 mcg via a metered dose inhaler (MDI) twice daily for 12 weeks

Arm title	MF/F MDI 400/10 mcg BID

Arm description:

Participants received mometasone Furoate 400 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Mometasone furoate 400 mcg/formoterol 10 mcg (MF/F) combination
Investigational medicinal product code	
Other name	SCH 418131
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

MF/F 400/10 mcg via a metered dose inhaler (MDI) twice daily for 12 weeks

Arm title	MF MDI 400 mcg BID

Arm description:

Participants received Mometasone Furoate 400 mcg taken twice daily for 12 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 400 mcg via metered dose inhaler twice daily for 12 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 200/10 mcg BID	MF/F MDI 400/10 mcg BID	MF MDI 400 mcg BID
Started	233	255	240
Completed	208	228	207
Not completed	25	27	33
Did not meet protocol eligibility	7	5	5
Consent withdrawn by subject	1	2	5
Adverse event, non-fatal	2	2	5
'Noncompliance with protocol '	3	9	3
Lost to follow-up	1	-	1
'Administrative '	-	1	1
Lack of efficacy	11	8	13

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 the trial.

Baseline characteristics

Reporting groups	
Reporting group title	MF/F MDI 200/10 mcg BID
Reporting group description:	
Participants received mometasone Furoate 200 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 12 weeks.	
Reporting group title	MF/F MDI 400/10 mcg BID
Reporting group description:	
Participants received mometasone Furoate 400 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 12 weeks.	
Reporting group title	MF MDI 400 mcg BID
Reporting group description:	
Participants received Mometasone Furoate 400 mcg taken twice daily for 12 weeks.	

Reporting group values	MF/F MDI 200/10 mcg BID	MF/F MDI 400/10 mcg BID	MF MDI 400 mcg BID
Number of subjects	233	255	240
Age categorical Units: Subjects			
<18 years	18	23	22
18 to <65 years	189	200	189
≥65 years	26	32	29
Age continuous Units: years			
arithmetic mean	48.4	47.7	47.8
standard deviation	± 16.3	± 15.6	± 16.4
Gender categorical Units: Subjects			
Female	135	138	136
Male	98	117	104

Reporting group values	Total		
Number of subjects	728		
Age categorical Units: Subjects			
<18 years	63		
18 to <65 years	578		
≥65 years	87		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	409		
Male	319		

End points

End points reporting groups

Reporting group title	OL MF MDI 400 MCG BID
Reporting group description:	
Participants received 2 to 3 weeks (approximately) of open-label, run-in medication with MF MDI 400 mcg BID prior to the 12-week double-blind treatment period.	
Reporting group title	MF/F MDI 200/10 mcg BID
Reporting group description:	
Participants received mometasone Furoate 200 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 12 weeks.	
Reporting group title	MF/F MDI 400/10 mcg BID
Reporting group description:	
Participants received mometasone Furoate 400 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 12 weeks.	
Reporting group title	MF MDI 400 mcg BID
Reporting group description:	
Participants received Mometasone Furoate 400 mcg taken twice daily for 12 weeks.	

Primary: LS Mean AUC [0-12 Hours] of the Change From Baseline to Week 12 in FEV1

End point title	LS Mean AUC [0-12 Hours] of the Change From Baseline to Week 12 in FEV1
End point description:	
Spirometry was performed to measure FEV1. 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 versus MF. Standard deviation was pooled.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	MF/F MDI 200/10 mcg BID	MF/F MDI 400/10 mcg BID	MF MDI 400 mcg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204[1]	231[2]	211[3]	
Units: Liter x hour				
least squares mean (standard deviation)	3.59 (± 3.63)	4.19 (± 3.63)	2.04 (± 3.63)	

Notes:

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

[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).

Statistical analyses

Statistical analysis title	FEV1(AUC): MF/F MDI 200/10 mcg vs. MF MDI 400 mcg

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 200/10 mcg BID v MF MDI 400 mcg BID
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	FEV1(AUC): MF/F MDI 400/10 mcg vs. MF MDI 400 mcg

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 400/10 mcg BID v MF MDI 400 mcg BID
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Change From Baseline to Week 12 in Asthma Control Questionnaire (ACQ) Total Score

End point title	Change From Baseline to Week 12 in Asthma Control Questionnaire (ACQ) Total Score

End point description:

The ACQ is a simple questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. ACQ consists of seven questions each scaled from 0 (best case) to 6 (worst case). The ACQ Total score was the mean of the individual seven questions. The comparison was for MF/F versus placebo. Standard deviation was pooled.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	MF/F MDI 200/10 mcg BID	MF/F MDI 400/10 mcg BID	MF MDI 400 mcg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205[4]	222[5]	206[6]	
Units: Units on a Scale				
least squares mean (standard deviation)	-0.59 (± 0.63)	-0.58 (± 0.63)	-0.42 (± 0.63)	

Notes:

[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).

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ[S]) Total Score

End point title	Change From Baseline to Week 12 in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ[S]) Total Score

End point description:

The AQLQ(S) for patients 12 years and older is a modified version of the AQLQ(S) that was originally designed to measure functional impairments that were most important for adults only; it was slightly changed to include questions about school activities. The AQLQ(S) measures the following four domains: symptoms, emotional functioning, impact of environmental stimuli, and activity limitation. AQLQ(S) consists of 32 questions each scaled from 1 (worst case) to 7 (best case). The AQLQ(S) Total score was the mean of the individual 32 questions. The comparison was for MF/F versus placebo. Standard deviation was pooled.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	MF/F MDI 200/10 mcg BID	MF/F MDI 400/10 mcg BID	MF MDI 400 mcg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205[7]	223[8]	208[9]	
Units: Units on a Scale				
least squares mean (standard deviation)	0.61 (± 0.7)	0.51 (± 0.7)	0.5 (± 0.7)	

Notes:

[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

No statistical analyses for this end point

Secondary: Change From Baseline in Proportion of Nights Across the Treatment Period With Nocturnal Awakenings Due to Asthma That 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 That Require Use of Short-Acting Beta Agonists (SABA)

End point description:

Baseline was 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 versus placebo. Standard deviation was pooled.

End point type	Secondary

End point timeframe:

12-week Treatment Period

End point values	MF/F MDI 200/10 mcg BID	MF/F MDI 400/10 mcg BID	MF MDI 400 mcg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233[10]	255[11]	239[12]	
Units: Proportion of nights				
least squares mean (standard deviation)	-0.1 (± 0.17)	-0.1 (± 0.17)	-0.05 (± 0.17)	

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).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Open-Label Run-In + DB Treatment Period (Day -21 to Week 12)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups	
Reporting group title	OL MF MDI 400 MCG BID
Reporting group description: Participants received 2 to 3 weeks (approximately) of open-label, run-in medication with MF MDI 400 mcg BID prior to the 12-week double-blind treatment period.	
Reporting group title	MF MDI 400 MCG BID
Reporting group description: Participants received Mometasone Furoate 400 mcg taken twice daily for 12 weeks.	
Reporting group title	MF/F MDI 400/10 MCG BID
Reporting group description: Participants received mometasone Furoate 400 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 12 weeks.	
Reporting group title	MF/F MDI 200/10 MCG BID
Reporting group description: Participants received mometasone Furoate 200 mcg and formoterol 10 mcg fixed dose combination taken twice daily for 12 weeks.	

Serious adverse events	OL MF MDI 400 MCG BID	MF MDI 400 MCG BID	MF/F MDI 400/10 MCG BID
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 834 (0.24%)	3 / 240 (1.25%)	2 / 255 (0.78%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine Aminotransferase* Increased			
subjects affected / exposed	1 / 834 (0.12%)	0 / 240 (0.00%)	0 / 255 (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
Aspartate Aminotransferase* Increased			
subjects affected / exposed	1 / 834 (0.12%)	0 / 240 (0.00%)	0 / 255 (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
Injury, poisoning and procedural			

complications			
Drug Exposure During Pregnancy			
subjects affected / exposed	0 / 834 (0.00%)	0 / 240 (0.00%)	0 / 255 (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
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 834 (0.00%)	0 / 240 (0.00%)	0 / 255 (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			
Chest Pain			
subjects affected / exposed	0 / 834 (0.00%)	1 / 240 (0.42%)	0 / 255 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 834 (0.00%)	0 / 240 (0.00%)	0 / 255 (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
Colitis Ulcerative			
subjects affected / exposed	0 / 834 (0.00%)	1 / 240 (0.42%)	0 / 255 (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
Colonic Polyp			
subjects affected / exposed	0 / 834 (0.00%)	1 / 240 (0.42%)	0 / 255 (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
Diarrhoea			
subjects affected / exposed	1 / 834 (0.12%)	0 / 240 (0.00%)	0 / 255 (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 / 834 (0.00%)	0 / 240 (0.00%)	1 / 255 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 834 (0.00%)	1 / 240 (0.42%)	0 / 255 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide Attempt			
subjects affected / exposed	0 / 834 (0.00%)	0 / 240 (0.00%)	0 / 255 (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
Renal and urinary disorders			
Renal Artery Stenosis			
subjects affected / exposed	0 / 834 (0.00%)	0 / 240 (0.00%)	1 / 255 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 834 (0.12%)	0 / 240 (0.00%)	0 / 255 (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	MF/F MDI 200/10 MCG BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 233 (1.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine Aminotransferase* Increased			
subjects affected / exposed	0 / 233 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate Aminotransferase* Increased			

subjects affected / exposed	0 / 233 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Drug Exposure During Pregnancy			
subjects affected / exposed	1 / 233 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	1 / 233 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 233 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 233 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis Ulcerative			
subjects affected / exposed	0 / 233 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colonic Polyp			
subjects affected / exposed	0 / 233 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	0 / 233 (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	0 / 233 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 233 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide Attempt			
subjects affected / exposed	1 / 233 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Artery Stenosis			
subjects affected / exposed	0 / 233 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 233 (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	OL MF MDI 400 MCG BID	MF MDI 400 MCG BID	MF/F MDI 400/10 MCG BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 834 (0.72%)	13 / 240 (5.42%)	12 / 255 (4.71%)
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 834 (0.72%) 6	13 / 240 (5.42%) 14	12 / 255 (4.71%) 13

Non-serious adverse events	MF/F MDI 200/10 MCG BID		
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 233 (3.43%)		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 233 (3.43%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2006	P04431 Amendment 1 added an additional treatment arm (MF/F 200/10 mcg BID) to the study, which increased study enrollment from 414 to 621. Amendment 1 also changed the primary analysis endpoint from Week 1 to Week 12 (which changed the primary objective) and revised the secondary objectives to include assessment of asthma control by ACQ, AQLQ(S), and proportion of nocturnal awakenings due to asthma which require use of SABA. Revision to the Statistical Analysis Plan was also required to address these changes.
27 December 2007	Amendment 2 added a Screening Period separate from the open-label Run-in Period and added telephone contact between Visit 1 and Visit 2, and clarified that participants would NOT start taking open-label run-in medication until after the laboratory results were available and found to be clinically acceptable. Amendment 2 also clarified several eligibility criteria (including modifying the age limit for countries such as Russia where minors are not permitted in clinical studies) and discontinuation criteria. Finally, Amendment 2 revised the defined stability limit in the definition of asthma exacerbation (secondary efficacy endpoint).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported