Clinical trial results:
A 52-Week Efficacy and Safety Non-Inferiority Study of Fluticasone Propionate/Salmeterol 250/50 mcg BID Delivered by Dry Powder Inhaler (DISKUS®) Versus Mometasone Furoate/Formoterol Fumarate 200/10 mcg BID Delivered by Pressurized Metered-Dose Inhaler in Persistent Asthmatics Previously Treated with Medium Doses of Inhaled Glucocorticosteroids

Summary

EudraCT number	2006-004169-33
Trial protocol	FI EE LT LV CZ DE SK NL
Global end of trial date	19 November 2008

Results information

Result version number	v1 (current)
This version publication date	05 April 2016
First version publication date	03 June 2015

Trial information

Trial identification

Sponsor protocol code	P04705

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00424008
WHO universal trial number (UTN)	-
Other trial identifiers	MK-0887A-116: 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	19 November 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 November 2008
Global end of trial reached?	Yes
Global end of trial date	19 November 2008
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority between mometasone furoate/formoterol fumarate (MF/F) metered-dose inhaler (MDI) 200/10 mcg twice daily (BID) and fluticasone propionate/salmeterol (F/SC) dry powder inhaler (DPI) 250/50 mcg BID on the effect of lung function after 12 weeks of treatment, in participants with persistent asthma requiring maintenance treatment on medium doses of inhaled glucocorticosteroids.

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 short-acting Beta 2-agonist (SABA, albuterol MDI or salbutamol MDI) rescue medication for the treatment of asthma symptoms and with oral prednisone/prednisolone for acute self-administration at home.

Background therapy:

Participants were provided with short-acting Beta 2-agonist (SABA, albuterol MDI or salbutamol MDI) rescue medication for the treatment of asthma symptoms and with oral prednisone/prednisolone for acute self-administration at home.

Evidence for comparator: -

Actual start date of recruitment	09 April 2007
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	Canada: 29
Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Costa Rica: 60
Country: Number of subjects enrolled	Ecuador: 17
Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Slovakia: 42

Country: Number of subjects enrolled	Czech Republic: 108
Country: Number of subjects enrolled	Estonia: 13
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Latvia: 18
Country: Number of subjects enrolled	Lithuania: 15
Country: Number of subjects enrolled	Serbia: 30
Country: Number of subjects enrolled	Ukraine: 139
Country: Number of subjects enrolled	United States: 117
Worldwide total number of subjects	722
EEA total number of subjects	236

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)	40
Adults (18-64 years)	629
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants screened were adolescents (≥12 years of age) or adults who had persistent asthma that was previously treated with medium doses of inhaled glucocorticosteroids.

Period 1

Period 1 title	52-Week Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

This was an open-label, evaluator-blind randomized trial.

Arms

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

Arm description:

Participants received MF/F MDI 200/100 mcg BID for up to 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Mometasone Furoate/Formoterol Fumarate
Investigational medicinal product code	
Other name	SCH 418131
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

MF/F MDI 200/10 mcg (two inhalations of 100/5 mcg inhaler) BID for up to 52 weeks

Arm title	F/SC DPI 250/50 mcg BID

Arm description:

Participants received F/SC DPI 250/50 mcg BID for up to 52 weeks.

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

Dosage and administration details:

F/SC DPI 250/50 mcg BID for up to 52 weeks.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an open-label, evaluator-blind randomized trial.

Number of subjects in period 1	MF/F MDI 200/10 mcg BID	F/SC DPI 250/50 mcg BID
Started	371	351
Treated	365	349
Completed	18	14
Not completed	353	337
Did not meet protocol eligibility	16	21
Consent withdrawn by subject	5	8
Administrative	266	257
Adverse event, non-fatal	8	6
Lost to follow-up	1	2
Not treated	4	2
Lack of efficacy	40	34
Protocol deviation	13	7

Baseline characteristics

Reporting groups	
Reporting group title	MF/F MDI 200/10 mcg BID
Reporting group description:	
Participants received MF/F MDI 200/100 mcg BID for up to 52 weeks.	
Reporting group title	F/SC DPI 250/50 mcg BID
Reporting group description:	
Participants received F/SC DPI 250/50 mcg BID for up to 52 weeks.	

Reporting group values	MF/F MDI 200/10 mcg BID	F/SC DPI 250/50 mcg BID	Total
Number of subjects	371	351	722
Age categorical Units: Subjects			
Adolescents (12-17 years)	22	18	40
Adults (18-64 years)	321	308	629
From 65-84 years	28	25	53
Gender categorical Units: Subjects			
Female	239	220	459
Male	132	131	263
Asthma Control Questionnaire (ACQ) Total Score			
The ACQ by Juniper et al. is a mean of 7 equally weighted composite scores; each scaled from 0=best case scenario to 6=worst case scenario on an integer scale. Composites include the following: How Often Woken by Asthma, How Bad Were Asthma Symptoms When You Woke, Activity Limitations, Shortness of Breath, Wheezing, Average Daily Short-Acting Beta 2-Agonist (SABA) Puffs, and physician-evaluated lung function. (n=350, 331)			
Units: score on a scale			
least squares mean	1.81	1.78	
standard deviation	± 0.63	± 0.63	-
Percentage of Days and Nights With No Symptoms of Asthma			
For each day of the evaluation period, symptoms were collected in the morning for the night's evaluation, and in the evening for the day's evaluation. Symptoms included coughing, wheezing and difficulty breathing, each integer-scaled from 0=none to 3=severe. A symptom-free day/night is defined as a combined score of 0 across the morning and evening evaluations. (n=364, 349)			
Units: Percentage of symptom-free days/nights			
least squares mean	0.19	0.18	
standard deviation	± 0.28	± 0.28	-

End points

End points reporting groups

Reporting group title	MF/F MDI 200/10 mcg BID
Reporting group description:	
Participants received MF/F MDI 200/100 mcg BID for up to 52 weeks.	
Reporting group title	F/SC DPI 250/50 mcg BID
Reporting group description:	
Participants received F/SC DPI 250/50 mcg BID for up to 52 weeks.	

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

End point title	The Area Under the Curve From 0 to 12 Hours [AUC(0-12 hr)] of the Change From Baseline to Week 12 Endpoint in Forced Expiratory Volume in One Second (FEV1)
End point description:	
The mean AUC(0-12 hr) of the change from Baseline to Week 12 in FEV1 was calculated. Baseline was the mean of two pre-dose FEV1 measurements on Day 1. Endpoint was the last post-Baseline non-missing FEV1 AUC(0-12 hr) result carried forward. 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 values	MF/F MDI 200/10 mcg BID	F/SC DPI 250/50 mcg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366[1]	346[2]		
Units: L x hr				
least squares mean (standard deviation)	3.43 (± 3.83)	3.24 (± 3.83)		

Notes:

[1] - Randomized participants who received ≥1 dose study drug and had Baseline and any post-Baseline data.

[2] - Randomized participants who received ≥1 dose study drug and had Baseline and any post-Baseline data.

Statistical analyses

Statistical analysis title	Change from Baseline ANCOVA - Baseline FEV1
Statistical analysis description:	
MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID

Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.007
Method	ANCOVA

Statistical analysis title	Change from Baseline ANCOVA - Treatment
Statistical analysis description:	
MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.54
Method	ANCOVA

Statistical analysis title	Change from Baseline ANCOVA - Site
Statistical analysis description:	
MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.008
Method	ANCOVA

Secondary: Onset-of-action Based on Change from Baseline FEV1 at the 5 Minute Pulmonary Function Test (PFT) Assessment on Day 1

End point title	Onset-of-action Based on Change from Baseline FEV1 at the 5 Minute Pulmonary Function Test (PFT) Assessment on Day 1

End point description:

PFTs, including FEV1, were done on Day 1. Evaluations included 30 min before and immediately before the first dose of study drug, the mean of which was Baseline, and at intervals from 5 min to 12 hr postdose. Onset of action was defined as statistically significant improvement of MF/F over F/SC in Change from Baseline FEV1 at the 5-min postdose evaluation on Day 1. The same series of PFTs was done at Week 12. Change from Baseline to Week 12 evalutions were calculated using the same Day 1 predose scores for Baseline. Post-Baseline LS means and pooled standard deviations were obtained from the ANCOVA model with treatment, site effects and Baseline FEV1 (Liters) as a covariate. Baseline LS means exclude the covariate.

End point type	Secondary

End point timeframe:

Baseline and 5 minutes postdose on Day 1

End point values	MF/F MDI 200/10 mcg BID	F/SC DPI 250/50 mcg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365[3]	348[4]		
Units: Liters				
least squares mean (standard deviation)	0.2 (± 0.2)	0.09 (± 0.2)		

Notes:

[3] - Randomized participants who received ≥1 dose study drug and had Baseline and any post-Baseline data.
[4] - Randomized participants who received ≥1 dose study drug and had Baseline and any post-Baseline data.

Statistical analyses

Statistical analysis title	Change from Baseline ANCOVA - Baseline FEV1
Statistical analysis description:	
MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	ANCOVA

Statistical analysis title	Change from Baseline ANCOVA - Treatment
Statistical analysis description:	
MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Change from Baseline ANCOVA - Site
Statistical analysis description:	
MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Change from Baseline in Asthma Control Questionnaire (ACQ) Total

Score at Week 12 Endpoint

End point title	Change from Baseline in Asthma Control Questionnaire (ACQ) Total Score at Week 12 Endpoint

End point description:

The ACQ by Juniper et al. is a mean of 7 equally weighted composite scores; each scaled from 0=best case scenario to 6=worst case scenario on an integer scale. Composites include the following: How Often Woken by Asthma, How Bad Were Asthma Symptoms When You Woke, Activity Limitations, Shortness of Breath, Wheezing, Average Daily Short-Acting Beta 2-Agonist (SABA) Puffs, and physician-evaluated lung function. With the exception of physician-evaluated lung function collected at the visit, evaluations were over the last week recall period. Endpoint was the last post-Baseline non-missing ACQ result carried forward. Post-Baseline LS means and pooled standard deviations were obtained from the ANCOVA model with treatment, site effects and the Baseline ACQ score as a covariate. Baseline LS means exclude the covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	MF/F MDI 200/10 mcg BID	F/SC DPI 250/50 mcg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350[5]	331[6]		
Units: Score on a scale				
least squares mean (standard deviation)	-0.65 (± 0.61)	-0.65 (± 0.61)		

Notes:

[5] - Randomized participants who received ≥1 dose study drug and had Baseline and any post-Baseline data.

[6] - Randomized participants who received ≥1 dose study drug and had Baseline and any post-Baseline data.

Statistical analyses

Statistical analysis title	Change from Baseline ANCOVA - Baseline ACQ Score

Statistical analysis description:

MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value

Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	681
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Change from Baseline ANCOVA - Treatment

Statistical analysis description:

MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value

Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID

Number of subjects included in analysis	681
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.925
Method	ANCOVA

Statistical analysis title	Change from Baseline ANCOVA - Site

Statistical analysis description:

MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value

Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	681
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANCOVA

Secondary: Change from Baseline in the Percentage of Days and Nights With No Symptoms of Asthma

End point title	Change from Baseline in the Percentage of Days and Nights With No Symptoms of Asthma

End point description:

For each day of the evaluation period, symptoms were collected in the morning for the night's evaluation, and in the evening for the day's evaluation. Symptoms included coughing, wheezing and difficulty breathing, each integer-scaled from 0=none to 3=severe. A symptom-free day/night is defined as a combined score of 0 across the morning and evening evaluations. The percentage of 0 scores across the Baseline period and across the 12-week treatment period were calculated to determine the overall percentage of symptom-free days/nights for each of these periods. Post-Baseline LS means and pooled standard deviations were obtained from the ANCOVA model with treatment, site effects and the Baseline as a covariate. Baseline LS means exclude the covariate.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	MF/F MDI 200/10 mcg BID	F/SC DPI 250/50 mcg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	364[7]	349[8]		
Units: Percentage of symptom-free days/nights				
least squares mean (standard deviation)	0.24 (± 0.32)	0.25 (± 0.32)		

Notes:

[7] - Randomized participants who received ≥1 dose study drug and had Baseline and any post-Baseline data.

[8] - Randomized participants who received ≥1 dose study drug and had Baseline and any post-Baseline data.

Statistical analyses

Statistical analysis title	Change from Baseline ANCOVA - Baseline Value
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Change from Baseline ANCOVA - Treatment
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.628
Method	ANCOVA

Statistical analysis title	Change from Baseline ANCOVA - Site
Statistical analysis description: MF/F MDI 200/10 mcg BID vs. F/SC DPI 250/50 mcg BID pairwise comparison p-value	
Comparison groups	MF/F MDI 200/10 mcg BID v F/SC DPI 250/50 mcg BID
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 52 weeks	
Adverse event reporting additional description:	
The safety population consists of all participants who received ≥1 dose of study drug.	
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 received MF/F MDI 200/100 mcg BID for up to 52 weeks.	
Reporting group title	F/SC DPI 250/50 mcg BID
Reporting group description:	
Participants received F/SC DPI 250/50 mcg BID for up to 52 weeks.	

Serious adverse events	MF/F MDI 200/10 mcg BID	F/SC DPI 250/50 mcg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 371 (1.62%)	8 / 351 (2.28%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Skin Injury			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Extrasystoles			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 371 (0.27%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Back Pain			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 371 (0.00%)	1 / 351 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	1 / 371 (0.27%)	0 / 351 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	MF/F MDI 200/10 mcg BID	F/SC DPI 250/50 mcg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 371 (22.91%)	77 / 351 (21.94%)	
Nervous system disorders			
Headache			
subjects affected / exposed	42 / 371 (11.32%)	45 / 351 (12.82%)	
occurrences (all)	109	88	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 371 (8.89%)	24 / 351 (6.84%)	
occurrences (all)	38	27	
Upper Respiratory Tract Infection			
subjects affected / exposed	25 / 371 (6.74%)	16 / 351 (4.56%)	
occurrences (all)	31	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2008	Amendment 01: Added a Screening Period separate from the Open-label Run-in Period. The open-label run-in medication was to have been dispensed at Visit 1; however, it was now clearly stated that participants would NOT start taking open-label MF MDI (run-in medication) until after the laboratory results were available and found to be clinically acceptable. The participants were contacted by telephone and told to stop taking their own standard ICS or fixed dose combination (FDC) treatment the following morning, and start taking their run-in study medication at that time. Participants with unacceptable laboratory results were not to be allowed to continue in the study and were required to have a termination visit. Additional clarifications were added to Selection Criteria. To reflect various Ethics Committees and Competent Authorities requirements, the age of participants in the study was also modified for the Czech Republic, Finland, Estonia, Germany, Lithuania, Russia, and Ukraine. The study discontinuation criteria were also further clarified to make evident that participants requiring the use of systemic corticosteroids, including oral prednisone/prednisolone during the study would be discontinued.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 November 2008	The sponsor closed the study early, at 12 weeks treatment, for reasons that were not safety related. No efficacy analysis of data collected beyond 12 weeks of treatment was performed. All safety data were examined regardless of treatment duration.	-

Notes:

Limitations and caveats

None reported