Clinical trial results:
A 12-Week, Randomized, Placebo-Controlled, Dose-Ranging, Efficacy and Safety Study of Mometasone Furoate Metered Dose Inhaler in the Treatment of Children Ages 5 to 11 Years With Persistent Asthma

Summary

EudraCT number	2008-007504-28
Trial protocol	LV EE HU PL GR BG
Global end of trial date	29 January 2015

Results information

Result version number	v2 (current)
This version publication date	05 March 2016
First version publication date	25 July 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	P04223

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01502371
WHO universal trial number (UTN)	-
Other trial identifiers	MK-0887-086: Merck protocol number, SCH 032088 P04223: 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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2015
Global end of trial reached?	Yes
Global end of trial date	29 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the dose-related efficacy by evaluating morning lung function at the end of the dosing interval (AM pre-dose percent predicted forced expiratory volume in one second [FEV1]) after 12 weeks of treatment, of three doses (50 mcg, 100 mcg, and 200 mcg) of mometasone furoate (MF) metered dose inhaler (MDI) twice a day (BID) compared with placebo in children 5 to 11 years of age, inclusive, with persistent asthma.

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 measure defined for this individual study was in place for the protection of trial subjects: participants were provided with a short-acting ß-agonist (albuterol MDI 90 mcg in the United States [US], salbutamol MDI 100 mcg non-US) as rescue therapy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2012
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	Poland: 64
Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Estonia: 19
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 71
Country: Number of subjects enrolled	Latvia: 20
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	Colombia: 28
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Guatemala: 92
Country: Number of subjects enrolled	Mexico: 20
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Ukraine: 32
Country: Number of subjects enrolled	United States: 91
Country: Number of subjects enrolled	Romania: 41

Country: Number of subjects enrolled	Russian Federation: 24
Worldwide total number of subjects	578
EEA total number of subjects	265

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)	577
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants aged 5 to 11 years, inclusive, who had persistent asthma were screened for this study.

Period 1

Period 1 title	Treatment Period (12 weeks) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	MF MDI 50 mcg BID

Arm description:

Participants receive MF MDI 25 mcg X 2 inhalations (50 mcg total dose) BID plus Placebo dry powder inhaler (DPI) X 1 inhalation in the evening for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Mometasone furoate metered dose inhaler (MF MDI)
Investigational medicinal product code	
Other name	SCH 032088, MK-0887
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MF MDI 25 mcg, 50 mcg or 100 mcg X 2 inhalations BID for 12 weeks

Investigational medicinal product name	Placebo dry powder inhaler (Placebo DPI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo DPI X 1 inhalation in the evening for 12 weeks

Arm title	MF MDI 100 mcg BID

Arm description:

Participants receive MF MDI 50 mcg X 2 inhalations (100 mcg total dose) BID plus Placebo DPI X 1 inhalation in the evening for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo dry powder inhaler (Placebo DPI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo DPI X 1 inhalation in the evening for 12 weeks

Investigational medicinal product name	Mometasone furoate metered dose inhaler (MF MDI)
Investigational medicinal product code	
Other name	SCH 032088, MK-0887

Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MF MDI 25 mcg, 50 mcg or 100 mcg X 2 inhalations BID for 12 weeks

Arm title	MF MDI 200 mcg BID

Arm description:

Participants receive MF MDI 100 mcg X 2 inhalations (200 mcg total dose) BID plus Placebo DPI X 1 inhalation in the evening for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo dry powder inhaler (Placebo DPI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo DPI X 1 inhalation in the evening for 12 weeks

Investigational medicinal product name	Mometasone furoate metered dose inhaler (MF MDI)
Investigational medicinal product code	
Other name	SCH 032088, MK-0887
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MF MDI 25 mcg, 50 mcg or 100 mcg X 2 inhalations BID for 12 weeks

Arm title	MF DPI 100 mcg QD

Arm description:

Participants receive Placebo MDI X 2 inhalations BID plus MF DPI 100 mcg X 1 inhalation once daily in the evening for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Placebo MDI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo MDI X 2 inhalations BID for 12 weeks

Investigational medicinal product name	Mometasone furoate dry powder inhaler (MF DPI)
Investigational medicinal product code	
Other name	SCH 032088, MK-0887
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MF DPI 100 mcg X 1 inhalation once daily in the evening for 12 weeks

Arm title	Placebo

Arm description:

Participants receive Placebo MDI X 2 inhalations BID plus Placebo DPI X 1 inhalation once daily in the evening for 12 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo dry powder inhaler (Placebo DPI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo DPI X 1 inhalation in the evening for 12 weeks

Investigational medicinal product name	Placebo MDI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo MDI X 2 inhalations BID for 12 weeks

Number of subjects in period 1	MF MDI 50 mcg BID	MF MDI 100 mcg BID	MF MDI 200 mcg BID
Started	120	113	108
Completed	79	81	83
Not completed	41	32	25
Physician decision	3	-	-
Consent withdrawn by subject	1	2	1
Treatment failure	22	20	12
Adverse event, non-fatal	2	1	-
Technical problems	1	-	2
Excluded medication	-	1	1
Noncompliance with study drug	-	-	1
Lack of efficacy	3	3	2
Protocol deviation	9	5	6

Number of subjects in period 1	MF DPI 100 mcg QD	Placebo
Started	125	112
Completed	88	60
Not completed	37	52
Physician decision	-	1
Consent withdrawn by subject	1	1
Treatment failure	19	30
Adverse event, non-fatal	4	3
Technical problems	4	1
Excluded medication	-	1
Noncompliance with study drug	2	1
Lack of efficacy	2	4

Protocol deviation	5	10

Baseline characteristics

Reporting groups	
Reporting group title	MF MDI 50 mcg BID
Reporting group description:	
Participants receive MF MDI 25 mcg X 2 inhalations (50 mcg total dose) BID plus Placebo dry powder inhaler (DPI) X 1 inhalation in the evening for 12 weeks.	
Reporting group title	MF MDI 100 mcg BID
Reporting group description:	
Participants receive MF MDI 50 mcg X 2 inhalations (100 mcg total dose) BID plus Placebo DPI X 1 inhalation in the evening for 12 weeks.	
Reporting group title	MF MDI 200 mcg BID
Reporting group description:	
Participants receive MF MDI 100 mcg X 2 inhalations (200 mcg total dose) BID plus Placebo DPI X 1 inhalation in the evening for 12 weeks.	
Reporting group title	MF DPI 100 mcg QD
Reporting group description:	
Participants receive Placebo MDI X 2 inhalations BID plus MF DPI 100 mcg X 1 inhalation once daily in the evening for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants receive Placebo MDI X 2 inhalations BID plus Placebo DPI X 1 inhalation once daily in the evening for 12 weeks.	

Reporting group values	MF MDI 50 mcg BID	MF MDI 100 mcg BID	MF MDI 200 mcg BID
Number of subjects	120	113	108
Age categorical Units: Subjects			
Children (2-11 years)	120	113	108
Adolescents (12-17 years)	0	0	0
Age continuous Units: years			
arithmetic mean	8.7	8.6	8.7
standard deviation	± 1.7	± 1.9	± 1.7
Gender categorical Units: Subjects			
Female	51	44	59
Male	69	69	49

Reporting group values	MF DPI 100 mcg QD	Placebo	Total
Number of subjects	125	112	578
Age categorical Units: Subjects			
Children (2-11 years)	125	111	577
Adolescents (12-17 years)	0	1	1
Age continuous Units: years			
arithmetic mean	8.7	9	
standard deviation	± 1.7	± 1.7	-

Gender categorical Units: Subjects			
Female	48	30	232
Male	77	82	346

End points

End points reporting groups

Reporting group title	MF MDI 50 mcg BID
Reporting group description:	
Participants receive MF MDI 25 mcg X 2 inhalations (50 mcg total dose) BID plus Placebo dry powder inhaler (DPI) X 1 inhalation in the evening for 12 weeks.	
Reporting group title	MF MDI 100 mcg BID
Reporting group description:	
Participants receive MF MDI 50 mcg X 2 inhalations (100 mcg total dose) BID plus Placebo DPI X 1 inhalation in the evening for 12 weeks.	
Reporting group title	MF MDI 200 mcg BID
Reporting group description:	
Participants receive MF MDI 100 mcg X 2 inhalations (200 mcg total dose) BID plus Placebo DPI X 1 inhalation in the evening for 12 weeks.	
Reporting group title	MF DPI 100 mcg QD
Reporting group description:	
Participants receive Placebo MDI X 2 inhalations BID plus MF DPI 100 mcg X 1 inhalation once daily in the evening for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants receive Placebo MDI X 2 inhalations BID plus Placebo DPI X 1 inhalation once daily in the evening for 12 weeks.	

Primary: Change from Baseline in Percent Predicted Morning (AM) Forced Expiratory Volume in 1 Second (FEV1)

End point title	Change from Baseline in Percent Predicted Morning (AM) Forced Expiratory Volume in 1 Second (FEV1)
End point description:	
FEV1 is the amount of air, measured in liters, forcibly exhaled in 1 second. Pulmonary function tests were to be performed by participants in the morning before dosing. The percent predicted FEV1 equals the participant's observed FEV1 divided by the participant's predicted FEV1 (determined by height and race) and converted to a percentage by multiplying by 100%.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	MF MDI 50 mcg BID	MF MDI 100 mcg BID	MF MDI 200 mcg BID	MF DPI 100 mcg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	114[1]	109[2]	105[3]	122[4]
Units: Percentage of Predicted FEV1				
least squares mean (confidence interval 95%)	4.52 (2.32 to 6.72)	6.95 (4.73 to 9.16)	6 (3.74 to 8.25)	3.13 (1.01 to 5.25)

Notes:

[1] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

[2] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

[3] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

[4] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	111[5]			
Units: Percentage of Predicted FEV1				
least squares mean (confidence interval 95%)	0.66 (-1.72 to 3.03)			

Notes:

[5] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

Statistical analyses

Statistical analysis title	MF MDI 50 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in percent predicted FEV1 at Week 12 - MF MDI 50 mcg BID vs. Placebo. Constrained longitudinal data analysis (cLDA) model method proposed by Liang and Zeger includes terms for treatment, time in weeks, age strata (ages 5-6, 7-11), treatment by time interaction and region (North America, Latin America and the European Union)

Comparison groups	MF MDI 50 mcg BID v Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	7.09

Statistical analysis title	MF MDI 100 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in percent predicted FEV1 at Week 12 - MF MDI 100 mcg BID vs. Placebo. cLDA model method proposed by Liang and Zeger includes terms for treatment, time in weeks, age strata (ages 5-6, 7-11), treatment by time interaction and region (North America, Latin America and the European Union)

Comparison groups	MF MDI 100 mcg BID v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	6.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.05
upper limit	9.53

Statistical analysis title	MF MDI 200 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in percent predicted FEV1 at Week 12 - MF MDI 200 mcg BID vs. Placebo. cLDA model method proposed by Liang and Zeger includes terms for treatment, time in weeks, age strata (ages 5-6, 7-11), treatment by time interaction and region (North America, Latin America and the European Union)

Comparison groups	MF MDI 200 mcg BID v Placebo
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	5.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.07
upper limit	8.61

Statistical analysis title	MF MDI 50 mcg BID vs. MF DPI 100 mcg QD

Statistical analysis description:

Change from Baseline in percent predicted FEV1 at Week 12 - MF MDI 50 mcg BID vs. MF DPI 100 mcg QD. cLDA model method proposed by Liang and Zeger includes terms for treatment, time in weeks, age strata (ages 5-6, 7-11), treatment by time interaction and region (North America, Latin America and the European Union)

Comparison groups	MF MDI 50 mcg BID v MF DPI 100 mcg QD
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	4.44

Secondary: Change from Baseline in Morning (AM) Peak Expiratory Flow (PEF)	
End point title	Change from Baseline in Morning (AM) Peak Expiratory Flow (PEF)

End point description:

PEF, measured in liters, is the highest flow during exhalation. Participants recorded diary entries for PEF twice daily (in the AM upon rising and in the PM at bedtime).

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	MF MDI 50 mcg BID	MF MDI 100 mcg BID	MF MDI 200 mcg BID	MF DPI 100 mcg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	118[6]	112[7]	108[8]	123[9]
Units: liters per minute				
least squares mean (confidence interval 95%)	17.83 (5.35 to 30.3)	26.03 (13.55 to 38.51)	16.68 (4.5 to 28.86)	-0.92 (-12.82 to 10.99)

Notes:

[6] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

[7] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

[8] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

[9] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	111[10]			
Units: liters per minute				
least squares mean (confidence interval 95%)	-1.32 (-15.49 to 12.85)			

Notes:

[10] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

Statistical analyses

Statistical analysis title	MF MDI 50 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in AM PEF - MF MDI 50 mcg BID vs. Placebo. cLDA model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the European Union).

Comparison groups	MF MDI 50 mcg BID v Placebo
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	19.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	37.87

Statistical analysis title	MF MDI 200 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in AM PEF - MF MDI 200 mcg BID vs. Placebo. cLDA model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the European Union).

Comparison groups	MF MDI 200 mcg BID v Placebo
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	18.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	36.53

Statistical analysis title	MF MDI 100 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in AM PEF - MF MDI 100 mcg BID vs. Placebo. cLDA model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the European Union).

Comparison groups	MF MDI 100 mcg BID v Placebo
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	27.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.63
upper limit	46.08

Secondary: Change from Baseline in Standardized Paediatric Asthma Quality of Life

Questionnaire Score (PAQLQ[S]) Total Score	
End point title	Change from Baseline in Standardized Paediatric Asthma Quality of Life Questionnaire Score (PAQLQ[S]) Total Score

End point description:

The PAQLQ(S) consists of 23 questions in 3 categories: Symptoms (10 items), Activity Limitations (5 items) and Emotional Function (8 items). Responses are based on a 7-point scale (7=not bothered at all to 1=extremely bothered). The PAQLQ(S) included only participants in participating countries in which a validated translated questionnaire was available.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	MF MDI 50 mcg BID	MF MDI 100 mcg BID	MF MDI 200 mcg BID	MF DPI 100 mcg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	111[11]	105[12]	101[13]	115[14]
Units: score on a scale				
least squares mean (confidence interval 95%)	0.35 (0.23 to 0.48)	0.38 (0.25 to 0.5)	0.44 (0.31 to 0.56)	0.47 (0.35 to 0.59)

Notes:

[11] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.
[12] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.
[13] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.
[14] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	102[15]			
Units: score on a scale				
least squares mean (confidence interval 95%)	0.26 (0.12 to 0.39)			

Notes:

[15] - All participants who received ≥1 study drug dose & had a baseline or ≥1 post-randomization value.

Statistical analyses

Statistical analysis title	MF MDI 50 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in PAQLQ(S) Total Score - MF MDI 50 mcg BID vs. Placebo. cLDA model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the European Union).

Comparison groups	MF MDI 50 mcg BID v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.27

Statistical analysis title	MF MDI 100 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in PAQLQ(S) Total Score - MF MDI 100 mcg BID vs. Placebo. cLDA model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the European Union).

Comparison groups	MF MDI 100 mcg BID v Placebo
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.178
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.3

Statistical analysis title	MF MDI 200 mcg BID vs. Placebo

Statistical analysis description:

Change from Baseline in PAQLQ(S) Total Score - MF MDI 200 mcg BID vs. Placebo. cLDA model includes terms for treatment, time in weeks, age strata (ages 5-6,7-11), treatment by time interaction and region (North America, Latin America, and the European Union).

Comparison groups	MF MDI 200 mcg BID v Placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	cLDA model
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.36

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 12 weeks	
Adverse event reporting additional description:	
The safety population consisted of all participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	MF MDI 50 mcg BID
Reporting group description:	
Participants receive MF MDI 25 mcg X 2 inhalations (50 mcg total dose) BID plus Placebo DPI X 1inhalation in the evening for 12 weeks.	
Reporting group title	MF MDI 100 mcg BID
Reporting group description:	
Participants receive MF MDI 50 mcg X 2 inhalations (100 mcg total dose) BID plus Placebo DPI X 1inhalation in the evening for 12 weeks.	
Reporting group title	MF MDI 200 mcg BID
Reporting group description:	
Participants receive MF MDI 100 mcg X 2 inhalations (200 mcg total dose) BID plus Placebo DPI X 1 inhalation in the evening for 12 weeks.	
Reporting group title	MF DPI 100 mcg QD PM
Reporting group description:	
Participants receive Placebo MDI X 2 inhalations BID plus MF DPI 100 mcg X 1 inhalation once daily in the evening for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants receive Placebo MDI X 2 inhalations BID plus Placebo DPI X 1 inhalation once daily in the evening for 12 weeks.	

Serious adverse events	MF MDI 50 mcg BID	MF MDI 100 mcg BID	MF MDI 200 mcg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 120 (1.67%)	1 / 113 (0.88%)	2 / 108 (1.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 120 (0.00%)	0 / 113 (0.00%)	0 / 108 (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
Gastrointestinal disorders			

Dyspepsia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 113 (0.88%)	0 / 108 (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
Enteritis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 113 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 120 (1.67%)	0 / 113 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 120 (0.00%)	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 113 (0.00%)	0 / 108 (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
Gastroenteritis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 113 (0.00%)	0 / 108 (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
Otitis media			
subjects affected / exposed	0 / 120 (0.00%)	0 / 113 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MF DPI 100 mcg QD PM	Placebo	
Total subjects affected by serious adverse events			

subjects affected / exposed	4 / 125 (3.20%)	2 / 112 (1.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 125 (0.80%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 125 (0.00%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 112 (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	0 / 125 (0.00%)	2 / 112 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 125 (0.00%)	0 / 112 (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	1 / 125 (0.80%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 125 (0.80%)	0 / 112 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 125 (0.00%)	0 / 112 (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	MF MDI 50 mcg BID	MF MDI 100 mcg BID	MF MDI 200 mcg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 120 (15.83%)	18 / 113 (15.93%)	18 / 108 (16.67%)
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	13 / 120 (10.83%)	13 / 113 (11.50%)	12 / 108 (11.11%)
occurrences (all)	18	19	19
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 120 (6.67%)	5 / 113 (4.42%)	7 / 108 (6.48%)
occurrences (all)	9	6	9

Non-serious adverse events	MF DPI 100 mcg QD PM	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 125 (12.80%)	19 / 112 (16.96%)	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	10 / 125 (8.00%)	13 / 112 (11.61%)	
occurrences (all)	14	19	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 125 (6.40%)	8 / 112 (7.14%)	
occurrences (all)	8	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2011	Amendment 02: Amendment 02 was developed prior to any participant being randomized. The primary reason for the protocol amendment was to remove the Interviewer-Administered Asthma Control Questionnaire (ACQ-IA) from the study and to clarify Events of Clinical Interest.
30 March 2012	Amendment 01: Amendment 01 was developed prior to any participant being randomized. The primary reason for the protocol amendment was to clarify text and update the protocol template.
13 September 2013	Amendment 03: The primary reason for Amendment 03 was to clarify and align sections throughout the protocol and to remove an analysis of covariance (ANCOVA) analysis originally proposed as a confirmatory analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported