# 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<br>Units: Subjects | | | |
| Children (2-11 years) | 120 | 113 | 108 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 8.7 | 8.6 | 8.7 |
| standard deviation | ± 1.7 | ± 1.9 | ± 1.7 |
| Gender categorical<br>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<br>Units: Subjects | | | |
| Children (2-11 years) | 125 | 111 | 577 |
| Adolescents (12-17 years) | 0 | 1 | 1 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 8.7 | 9 | |
| standard deviation | ± 1.7 | ± 1.7 | - |

| Gender categorical<br>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