



## Clinical trial results:

### A 26-Week Placebo-Controlled Efficacy and Safety Study of Mometasone Furoate/Formoterol Fumarate Combination Formulation Compared With Mometasone Furoate and Formoterol Monotherapy in Subjects with Persistent Asthma Previously Treated With Medium-Dose Inhaled Glucocorticosteroids

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2006-001578-25    |
| Trial protocol           | HU EE DK          |
| Global end of trial date | 23 September 2008 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 05 April 2016 |
| First version publication date | 09 May 2015   |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | P04334 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |                                     |
|------------------------------------|-------------------------------------|
| ISRCTN number                      | -                                   |
| ClinicalTrials.gov id (NCT number) | NCT00383240                         |
| WHO universal trial number (UTN)   | -                                   |
| Other trial identifiers            | MK-0887A-092: 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.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |

Notes:

#### Paediatric regulatory details

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-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                       | 23 September 2008 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 23 September 2008 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 23 September 2008 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

1. To determine the efficacy of mometasone furoate/formoterol (MF/F) metered-dose inhaler (MDI) 200/10 mcg twice each day (BID) compared with mometasone furoate (MF MDI 200 mcg BID), in order to assess the added benefit of formoterol (F MDI 10 mcg BID) to the combination.
2. To determine the efficiency of MF/F MDI 200/10 mcg BID compared with F MDI 10 mcg BID, in order to assess the benefit of the steroid component of the combination.

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 locally purchased short-acting  $\beta$ -agonist (SABA: albuterol MDI 90 mcg in the United States; salbutamol MDI 100 mcg outside of the United States) to treat asthma symptoms and were also provided with locally purchased oral prednisone/prednisolone for acute self-administration.

Background therapy:

Subjects were provided with locally purchased SABA (albuterol MDI 90 mcg in the United States; salbutamol MDI 100 mcg outside of the United States) to treat asthma symptoms and were also provided with locally purchased oral prednisone/prednisolone for acute self-administration.

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 28 September 2006 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Denmark: 1     |
| Country: Number of subjects enrolled | Estonia: 5     |
| Country: Number of subjects enrolled | Hungary: 86    |
| Country: Number of subjects enrolled | Canada: 6      |
| Country: Number of subjects enrolled | Colombia: 4    |
| Country: Number of subjects enrolled | Costa Rica: 22 |
| Country: Number of subjects enrolled | Croatia: 6     |
| Country: Number of subjects enrolled | Ecuador: 7     |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Guatemala: 17          |
| Country: Number of subjects enrolled | India: 58              |
| Country: Number of subjects enrolled | Mexico: 45             |
| Country: Number of subjects enrolled | Philippines: 47        |
| Country: Number of subjects enrolled | Poland: 113            |
| Country: Number of subjects enrolled | Russian Federation: 41 |
| Country: Number of subjects enrolled | Thailand: 6            |
| Country: Number of subjects enrolled | Ukraine: 53            |
| Country: Number of subjects enrolled | United States: 264     |
| Worldwide total number of subjects   | 781                    |
| EEA total number of subjects         | 211                    |

Notes:

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### 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)                 | 63  |
| Adults (18-64 years)                      | 677 |
| From 65 to 84 years                       | 41  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants screened for this study were 12 years of age or older, had a diagnosis of asthma of at least 12 months duration, were using a medium daily dose of inhaled corticosteroids (ICS) for at least 12 weeks and were on a stable ICS regimen for at least 2 weeks prior to Screening.

### Period 1

|                              |                                           |
|------------------------------|-------------------------------------------|
| Period 1 title               | 26-Week Treatment Period (overall period) |
| Is this the baseline period? | Yes                                       |
| Allocation method            | Randomised - controlled                   |
| Blinding used                | Double blind                              |
| Roles blinded                | Subject, Investigator                     |

### Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | MF/F MDI 200/10 mcg BID |

Arm description:

Participants receive MF/F MDI 200/10 mcg BID for up to 26 weeks

|                                        |                                        |
|----------------------------------------|----------------------------------------|
| Arm type                               | Experimental                           |
| Investigational medicinal product name | mometasone furoate/formoterol fumarate |
| Investigational medicinal product code |                                        |
| Other name                             | MK-0887A, SCH 418131                   |
| Pharmaceutical forms                   | Inhalation powder                      |
| Routes of administration               | Inhalation use                         |

Dosage and administration details:

MF/F MDI 200/10 mcg BID for up to 26 weeks

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | MF MDI 200 mcg BID |
|------------------|--------------------|

Arm description:

Participants receive MF MDI 200 mcg BID for up to 26 weeks

|                                        |                     |
|----------------------------------------|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | mometasone furoate  |
| Investigational medicinal product code |                     |
| Other name                             | MK-0887, SCH 032088 |
| Pharmaceutical forms                   | Inhalation powder   |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

MF MDI 200 mcg BID for up to 26 weeks

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | F MDI 10 mcg BID |
|------------------|------------------|

Arm description:

Participants receive F MDI 10 mcg BID for up to 26 weeks

|                                        |                     |
|----------------------------------------|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | formoterol fumarate |
| Investigational medicinal product code |                     |
| Other name                             | Foradil®, MK-5571   |
| Pharmaceutical forms                   | Inhalation powder   |
| Routes of administration               | Inhalation use      |

Dosage and administration details:  
F MDI 10 mcg BID for up to 26 weeks

|                                                                             |                   |
|-----------------------------------------------------------------------------|-------------------|
| <b>Arm title</b>                                                            | Placebo MDI BID   |
| Arm description:<br>Participants receive placebo MDI BID for up to 26 weeks |                   |
| Arm type                                                                    | Placebo           |
| Investigational medicinal product name                                      | placebo           |
| Investigational medicinal product code                                      |                   |
| Other name                                                                  |                   |
| Pharmaceutical forms                                                        | Inhalation powder |
| Routes of administration                                                    | Inhalation use    |

Dosage and administration details:  
Placebo MDI BID for up to 26 weeks

| <b>Number of subjects in period 1</b> | MF/F MDI 200/10 mcg BID | MF MDI 200 mcg BID | F MDI 10 mcg BID |
|---------------------------------------|-------------------------|--------------------|------------------|
| Started                               | 191                     | 192                | 202              |
| Treated                               | 191                     | 192                | 202              |
| Completed                             | 156                     | 159                | 117              |
| Not completed                         | 35                      | 33                 | 85               |
| Consent withdrawn by subject          | 6                       | 4                  | 11               |
| Administrative                        | 1                       | 1                  | -                |
| Adverse event, non-fatal              | 4                       | 6                  | 9                |
| Non-compliance with protocol          | 4                       | 5                  | 9                |
| Lost to follow-up                     | 3                       | -                  | -                |
| Lack of efficacy                      | 8                       | 13                 | 47               |
| Protocol deviation                    | 9                       | 4                  | 9                |

| <b>Number of subjects in period 1</b> | Placebo MDI BID |
|---------------------------------------|-----------------|
| Started                               | 196             |
| Treated                               | 195             |
| Completed                             | 119             |
| Not completed                         | 77              |
| Consent withdrawn by subject          | 13              |
| Administrative                        | -               |
| Adverse event, non-fatal              | 7               |
| Non-compliance with protocol          | 6               |
| Lost to follow-up                     | 2               |
| Lack of efficacy                      | 46              |

|                    |   |
|--------------------|---|
| Protocol deviation | 3 |
|--------------------|---|

## Baseline characteristics

### Reporting groups

|                                                                 |                         |
|-----------------------------------------------------------------|-------------------------|
| Reporting group title                                           | MF/F MDI 200/10 mcg BID |
| Reporting group description:                                    |                         |
| Participants receive MF/F MDI 200/10 mcg BID for up to 26 weeks |                         |
| Reporting group title                                           | MF MDI 200 mcg BID      |
| Reporting group description:                                    |                         |
| Participants receive MF MDI 200 mcg BID for up to 26 weeks      |                         |
| Reporting group title                                           | F MDI 10 mcg BID        |
| Reporting group description:                                    |                         |
| Participants receive F MDI 10 mcg BID for up to 26 weeks        |                         |
| Reporting group title                                           | Placebo MDI BID         |
| Reporting group description:                                    |                         |
| Participants receive placebo MDI BID for up to 26 weeks         |                         |

| Reporting group values    | MF/F MDI 200/10 mcg BID | MF MDI 200 mcg BID | F MDI 10 mcg BID |
|---------------------------|-------------------------|--------------------|------------------|
| Number of subjects        | 191                     | 192                | 202              |
| Age categorical           |                         |                    |                  |
| Units: Subjects           |                         |                    |                  |
| Adolescents (12-17 years) | 19                      | 10                 | 18               |
| Adults (18-64 years)      | 161                     | 173                | 174              |
| From 65-84 years          | 11                      | 9                  | 10               |
| Age continuous            |                         |                    |                  |
| Units: years              |                         |                    |                  |
| arithmetic mean           | 42.9                    | 42.8               | 41.9             |
| standard deviation        | ± 16.3                  | ± 14.9             | ± 15.3           |
| Gender categorical        |                         |                    |                  |
| Units: Subjects           |                         |                    |                  |
| Female                    | 97                      | 112                | 129              |
| Male                      | 94                      | 80                 | 73               |

| Reporting group values    | Placebo MDI BID | Total |  |
|---------------------------|-----------------|-------|--|
| Number of subjects        | 196             | 781   |  |
| Age categorical           |                 |       |  |
| Units: Subjects           |                 |       |  |
| Adolescents (12-17 years) | 16              | 63    |  |
| Adults (18-64 years)      | 169             | 677   |  |
| From 65-84 years          | 11              | 41    |  |
| Age continuous            |                 |       |  |
| Units: years              |                 |       |  |
| arithmetic mean           | 41.9            | -     |  |
| standard deviation        | ± 15.3          |       |  |
| Gender categorical        |                 |       |  |
| Units: Subjects           |                 |       |  |
| Female                    | 122             | 460   |  |
| Male                      | 74              | 321   |  |



## End points

### End points reporting groups

|                                                                 |                         |
|-----------------------------------------------------------------|-------------------------|
| Reporting group title                                           | MF/F MDI 200/10 mcg BID |
| Reporting group description:                                    |                         |
| Participants receive MF/F MDI 200/10 mcg BID for up to 26 weeks |                         |
| Reporting group title                                           | MF MDI 200 mcg BID      |
| Reporting group description:                                    |                         |
| Participants receive MF MDI 200 mcg BID for up to 26 weeks      |                         |
| Reporting group title                                           | F MDI 10 mcg BID        |
| Reporting group description:                                    |                         |
| Participants receive F MDI 10 mcg BID for up to 26 weeks        |                         |
| Reporting group title                                           | Placebo MDI BID         |
| Reporting group description:                                    |                         |
| Participants receive placebo MDI BID for up to 26 weeks         |                         |

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

|                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                          | Mean Area Under the Time Curve From 0 to 12 Hours (AUC[0-12h]) of Change From Baseline to Week 12 in Forced Expiratory Volume in One Second (FEV1) |
| End point description:                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                    |
| Baseline was the mean of two pre-dose FEV1 measurements on Day 1. Endpoint was the last post-Baseline non-missing FEV1 AUC(0-12h) result carried forward. Post-Baseline 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                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                    |

| End point values                        | MF/F MDI 200/10 mcg BID | MF MDI 200 mcg BID | F MDI 10 mcg BID   | Placebo MDI BID    |
|-----------------------------------------|-------------------------|--------------------|--------------------|--------------------|
| Subject group type                      | Reporting group         | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed             | 190 <sup>[1]</sup>      | 190 <sup>[2]</sup> | 202 <sup>[3]</sup> | 193 <sup>[4]</sup> |
| Units: liters x hours                   |                         |                    |                    |                    |
| least squares mean (standard deviation) | 3.19 (± 3.98)           | 1.31 (± 3.98)      | 1.6 (± 3.98)       | 0.51 (± 3.98)      |

Notes:

[1] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[2] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[3] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[4] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

### Statistical analyses

|                            |                                                |
|----------------------------|------------------------------------------------|
| Statistical analysis title | MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID |
|----------------------------|------------------------------------------------|

Statistical analysis description:

MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison P-value

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| Comparison groups                       | MF/F MDI 200/10 mcg BID v MF MDI 200 mcg BID |
| Number of subjects included in analysis | 380                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | < 0.001                                      |
| Method                                  | ANCOVA                                       |

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**Statistical analysis title**

MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID

Statistical analysis description:

MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value

|                                         |                                            |
|-----------------------------------------|--------------------------------------------|
| Comparison groups                       | MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID |
| Number of subjects included in analysis | 392                                        |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | < 0.001                                    |
| Method                                  | ANCOVA                                     |

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**Statistical analysis title**

MF/F MDI 200/10 mcg BID vs. Placebo MDI BID

Statistical analysis description:

MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison P-value

|                                         |                                           |
|-----------------------------------------|-------------------------------------------|
| Comparison groups                       | MF/F MDI 200/10 mcg BID v Placebo MDI BID |
| Number of subjects included in analysis | 383                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | < 0.001                                   |
| Method                                  | ANCOVA                                    |

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**Statistical analysis title**

MF MDI 200 mcg BID vs. F MDI 10 mcg BID

Statistical analysis description:

MF MDI 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value

|                                         |                                       |
|-----------------------------------------|---------------------------------------|
| Comparison groups                       | MF MDI 200 mcg BID v F MDI 10 mcg BID |
| Number of subjects included in analysis | 392                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.491                               |
| Method                                  | ANCOVA                                |

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**Statistical analysis title**

MF MDI 200 mcg BID vs. Placebo MDI BID

Statistical analysis description:

MF MDI 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Comparison groups                       | MF MDI 200 mcg BID v Placebo MDI BID |
| Number of subjects included in analysis | 383                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| P-value                                 | = 0.055                              |
| Method                                  | ANCOVA                               |

### Statistical analysis title

F MDI 10 mcg BID vs. Placebo MDI BID

Statistical analysis description:

F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| Comparison groups                       | F MDI 10 mcg BID v Placebo MDI BID |
| Number of subjects included in analysis | 395                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | = 0.008                            |
| Method                                  | ANCOVA                             |

### Primary: Number of Participants With At Least One Severe Asthma Exacerbation

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Number of Participants With At Least One Severe Asthma Exacerbation |
|-----------------|---------------------------------------------------------------------|

End point description:

A severe asthma exacerbation was defined as a clinically judged deterioration of asthma or a meaningful reduction in lung function based on any one of the following criteria during the Treatment Period: 1) A decrease in FEV1 (absolute value) below the Treatment Period stability limit at any visit during the Treatment Period. The Treatment Period stability limit was defined as 80% of the average of the two predose FEV1 measurements just prior to the first dose of randomized study medication. 2) A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment during the Treatment Period. The Treatment Period stability limit was defined as 70% of the respective mean AM or PM PEF obtained over the last 7 days immediately prior to receiving randomized study medication. 3) An occurrence of any clinical deterioration of asthma (i.e., asthma attack) that resulted in emergency treatment, hospitalization due to asthma or treatment with additional, excluded asthma medication.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

26 weeks

| End point values            | MF/F MDI 200/10 mcg BID | MF MDI 200 mcg BID | F MDI 10 mcg BID   | Placebo MDI BID    |
|-----------------------------|-------------------------|--------------------|--------------------|--------------------|
| Subject group type          | Reporting group         | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed | 191 <sup>[5]</sup>      | 192 <sup>[6]</sup> | 202 <sup>[7]</sup> | 196 <sup>[8]</sup> |
| Units: participants         | 58                      | 65                 | 109                | 109                |

Notes:

[5] - All randomized participants who took  $\geq 1$  study drug dose and were evaluable for this end point.

[6] - All randomized participants who took  $\geq 1$  study drug dose and were evaluable for this end point.

[7] - All randomized participants who took  $\geq 1$  study drug dose and were evaluable for this end point.

[8] - All randomized participants who took  $\geq 1$  study drug dose and were evaluable for this end point.

### Statistical analyses

|                                                                                                                 |                                                |
|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| <b>Statistical analysis title</b>                                                                               | MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID |
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison p-value |                                                |
| Comparison groups                                                                                               | MF/F MDI 200/10 mcg BID v MF MDI 200 mcg BID   |
| Number of subjects included in analysis                                                                         | 383                                            |
| Analysis specification                                                                                          | Pre-specified                                  |
| Analysis type                                                                                                   | superiority                                    |
| P-value                                                                                                         | = 0.565                                        |
| Method                                                                                                          | ANCOVA                                         |

|                                                                                                               |                                              |
|---------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>                                                                             | MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID |
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison p-value |                                              |
| Comparison groups                                                                                             | MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID   |
| Number of subjects included in analysis                                                                       | 393                                          |
| Analysis specification                                                                                        | Pre-specified                                |
| Analysis type                                                                                                 | superiority                                  |
| P-value                                                                                                       | < 0.001                                      |
| Method                                                                                                        | ANCOVA                                       |

|                                                                                                              |                                             |
|--------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b>                                                                            | MF/F MDI 200/10 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison p-value |                                             |
| Comparison groups                                                                                            | MF/F MDI 200/10 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                                      | 387                                         |
| Analysis specification                                                                                       | Pre-specified                               |
| Analysis type                                                                                                | superiority                                 |
| P-value                                                                                                      | < 0.001                                     |
| Method                                                                                                       | ANCOVA                                      |

|                                                                                                          |                                         |
|----------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>                                                                        | MF MDI 200 mcg BID vs. F MDI 10 mcg BID |
| Statistical analysis description:<br>MF MDI 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value |                                         |
| Comparison groups                                                                                        | MF MDI 200 mcg BID v F MDI 10 mcg BID   |

|                                         |               |
|-----------------------------------------|---------------|
| Number of subjects included in analysis | 394           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | < 0.001       |
| Method                                  | ANCOVA        |

|                                                                                                         |                                        |
|---------------------------------------------------------------------------------------------------------|----------------------------------------|
| <b>Statistical analysis title</b>                                                                       | MF MDI 200 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>MF MDI 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value |                                        |
| Comparison groups                                                                                       | MF MDI 200 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                                 | 388                                    |
| Analysis specification                                                                                  | Pre-specified                          |
| Analysis type                                                                                           | superiority                            |
| P-value                                                                                                 | < 0.001                                |
| Method                                                                                                  | ANCOVA                                 |

|                                                                                                       |                                      |
|-------------------------------------------------------------------------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>                                                                     | F MDI 10 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value |                                      |
| Comparison groups                                                                                     | F MDI 10 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                               | 398                                  |
| Analysis specification                                                                                | Pre-specified                        |
| Analysis type                                                                                         | superiority                          |
| P-value                                                                                               | = 0.967                              |
| Method                                                                                                | ANCOVA                               |

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

|                 |                                                                                                                      |
|-----------------|----------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline to Week 26 in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ[S]) Score |
|-----------------|----------------------------------------------------------------------------------------------------------------------|

End point description:

The AQLQ(S) consists of 32 questions covering 4 domains: symptoms, emotional functioning, impact of environmental stimuli and activity limitation. Responses to each question were to reflect participant experience over the previous 2 weeks and were scaled from 1 (worst case) to 7 (best case). End point was the last post-Baseline non-missing AQLQ(S) result carried forward. Post-Baseline LS means and pooled standard deviations were obtained from the ANCOVA model with treatment, site effects and the Baseline AQLQ(S) score as a covariate.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 26 End Point

| End point values                        | MF/F MDI 200/10 mcg BID | MF MDI 200 mcg BID  | F MDI 10 mcg BID    | Placebo MDI BID     |
|-----------------------------------------|-------------------------|---------------------|---------------------|---------------------|
| Subject group type                      | Reporting group         | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed             | 183 <sup>[9]</sup>      | 189 <sup>[10]</sup> | 187 <sup>[11]</sup> | 189 <sup>[12]</sup> |
| Units: score on a scale                 |                         |                     |                     |                     |
| least squares mean (standard deviation) | 0.49 (± 0.85)           | 0.37 (± 0.85)       | 0.05 (± 0.85)       | -0.01 (± 0.85)      |

Notes:

[9] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[10] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[11] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[12] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

## Statistical analyses

| Statistical analysis title                                                                                      | MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID |
|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison p-value |                                                |
| Comparison groups                                                                                               | MF MDI 200 mcg BID v MF/F MDI 200/10 mcg BID   |
| Number of subjects included in analysis                                                                         | 372                                            |
| Analysis specification                                                                                          | Pre-specified                                  |
| Analysis type                                                                                                   | superiority                                    |
| P-value                                                                                                         | = 0.174                                        |
| Method                                                                                                          | ANCOVA                                         |

| Statistical analysis title                                                                                    | MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID |
|---------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison p-value |                                              |
| Comparison groups                                                                                             | MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID   |
| Number of subjects included in analysis                                                                       | 370                                          |
| Analysis specification                                                                                        | Pre-specified                                |
| Analysis type                                                                                                 | superiority                                  |
| P-value                                                                                                       | < 0.001                                      |
| Method                                                                                                        | ANCOVA                                       |

| Statistical analysis title                                                                                   | MF/F MDI 200/10 mcg BID vs. Placebo MDI BID |
|--------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison p-value |                                             |
| Comparison groups                                                                                            | MF/F MDI 200/10 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                                      | 372                                         |
| Analysis specification                                                                                       | Pre-specified                               |
| Analysis type                                                                                                | superiority                                 |
| P-value                                                                                                      | < 0.001                                     |
| Method                                                                                                       | ANCOVA                                      |

|                                                                                                          |                                         |
|----------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>                                                                        | MF MDI 200 mcg BID vs. F MDI 10 mcg BID |
| Statistical analysis description:<br>MF MDI 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value |                                         |
| Comparison groups                                                                                        | MF MDI 200 mcg BID v F MDI 10 mcg BID   |
| Number of subjects included in analysis                                                                  | 376                                     |
| Analysis specification                                                                                   | Pre-specified                           |
| Analysis type                                                                                            | superiority                             |
| P-value                                                                                                  | < 0.001                                 |
| Method                                                                                                   | ANCOVA                                  |

|                                                                                                         |                                        |
|---------------------------------------------------------------------------------------------------------|----------------------------------------|
| <b>Statistical analysis title</b>                                                                       | MF MDI 200 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>MF MDI 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value |                                        |
| Comparison groups                                                                                       | MF MDI 200 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                                 | 378                                    |
| Analysis specification                                                                                  | Pre-specified                          |
| Analysis type                                                                                           | superiority                            |
| P-value                                                                                                 | < 0.001                                |
| Method                                                                                                  | ANCOVA                                 |

|                                                                                                       |                                      |
|-------------------------------------------------------------------------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>                                                                     | F MDI 10 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value |                                      |
| Comparison groups                                                                                     | F MDI 10 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                               | 376                                  |
| Analysis specification                                                                                | Pre-specified                        |
| Analysis type                                                                                         | superiority                          |
| P-value                                                                                               | = 0.521                              |
| Method                                                                                                | ANCOVA                               |

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

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

End point description:

The ACQ consists of 7 questions covering awakenings due to asthma, symptoms when awoken, activity limitations, shortness of breath, wheezing, number of puffs of SABA used and FEV1 % predicted. Responses to questions were to reflect participant experience over the previous week and were each scaled from 0 (best case) to 6 (worst case). End point 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.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 26 End Point

| <b>End point values</b>                 | MF/F MDI<br>200/10 mcg<br>BID | MF MDI 200<br>mcg BID | F MDI 10 mcg<br>BID | Placebo MDI<br>BID  |
|-----------------------------------------|-------------------------------|-----------------------|---------------------|---------------------|
| Subject group type                      | Reporting group               | Reporting group       | Reporting group     | Reporting group     |
| Number of subjects analysed             | 179 <sup>[13]</sup>           | 186 <sup>[14]</sup>   | 184 <sup>[15]</sup> | 187 <sup>[16]</sup> |
| Units: score on a scale                 |                               |                       |                     |                     |
| least squares mean (standard deviation) | -0.4 (± 0.74)                 | -0.23 (± 0.74)        | 0.11 (± 0.74)       | 0.14 (± 0.74)       |

Notes:

[13] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[14] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[15] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[16] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

### Statistical analyses

| <b>Statistical analysis title</b>                                                                               | MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID |
|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison p-value |                                                |
| Comparison groups                                                                                               | MF/F MDI 200/10 mcg BID v MF MDI 200 mcg BID   |
| Number of subjects included in analysis                                                                         | 365                                            |
| Analysis specification                                                                                          | Pre-specified                                  |
| Analysis type                                                                                                   | superiority                                    |
| P-value                                                                                                         | = 0.026                                        |
| Method                                                                                                          | ANCOVA                                         |

| <b>Statistical analysis title</b>                                                                             | MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID |
|---------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison p-value |                                              |
| Comparison groups                                                                                             | MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID   |
| Number of subjects included in analysis                                                                       | 363                                          |
| Analysis specification                                                                                        | Pre-specified                                |
| Analysis type                                                                                                 | superiority                                  |
| P-value                                                                                                       | < 0.001                                      |
| Method                                                                                                        | ANCOVA                                       |

| <b>Statistical analysis title</b>                                                                            | MF/F MDI 200/10 mcg BID vs. Placebo MDI BID |
|--------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison p-value |                                             |
| Comparison groups                                                                                            | MF/F MDI 200/10 mcg BID v Placebo MDI BID   |

|                                         |               |
|-----------------------------------------|---------------|
| Number of subjects included in analysis | 366           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | < 0.001       |
| Method                                  | ANCOVA        |

|                                                                                                          |                                         |
|----------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>                                                                        | MF MDI 200 mcg BID vs. F MDI 10 mcg BID |
| Statistical analysis description:<br>MF MDI 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value |                                         |
| Comparison groups                                                                                        | MF MDI 200 mcg BID v F MDI 10 mcg BID   |
| Number of subjects included in analysis                                                                  | 370                                     |
| Analysis specification                                                                                   | Pre-specified                           |
| Analysis type                                                                                            | superiority                             |
| P-value                                                                                                  | < 0.001                                 |
| Method                                                                                                   | ANCOVA                                  |

|                                                                                                         |                                        |
|---------------------------------------------------------------------------------------------------------|----------------------------------------|
| <b>Statistical analysis title</b>                                                                       | MF MDI 200 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>MF MDI 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value |                                        |
| Comparison groups                                                                                       | MF MDI 200 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                                 | 373                                    |
| Analysis specification                                                                                  | Pre-specified                          |
| Analysis type                                                                                           | superiority                            |
| P-value                                                                                                 | < 0.001                                |
| Method                                                                                                  | ANCOVA                                 |

|                                                                                                       |                                      |
|-------------------------------------------------------------------------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>                                                                     | F MDI 10 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value |                                      |
| Comparison groups                                                                                     | F MDI 10 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                               | 371                                  |
| Analysis specification                                                                                | Pre-specified                        |
| Analysis type                                                                                         | superiority                          |
| P-value                                                                                               | = 0.738                              |
| Method                                                                                                | ANCOVA                               |

## **Secondary: Change from Baseline Across the Treatment Period in Percentage of Nights With Nocturnal Awakenings Due to Asthma that Require Use of SABA**

|                 |                                                                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline Across the Treatment Period in Percentage of Nights With Nocturnal Awakenings Due to Asthma that Require Use of SABA |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|

**End point description:**

Baseline percentage of nights with nocturnal awakenings that required use of SABA included data from the last week before first dose of randomized study drug. End point percentage included data from the entire 26-week Treatment Period. Post-Baseline LS means and pooled standard deviations were obtained from the ANCOVA model with treatment, site effects and the Baseline percentage as a covariate.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

Baseline and 26-week Treatment Period End Point

| End point values                          | MF/F MDI 200/10 mcg BID | MF MDI 200 mcg BID  | F MDI 10 mcg BID    | Placebo MDI BID     |
|-------------------------------------------|-------------------------|---------------------|---------------------|---------------------|
| Subject group type                        | Reporting group         | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed               | 186 <sup>[17]</sup>     | 191 <sup>[18]</sup> | 199 <sup>[19]</sup> | 194 <sup>[20]</sup> |
| Units: percentage of nocturnal awakenings |                         |                     |                     |                     |
| least squares mean (standard deviation)   | -0.08 (± 0.17)          | -0.05 (± 0.17)      | 0.01 (± 0.17)       | 0 (± 0.17)          |

**Notes:**

[17] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[18] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[19] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

[20] - All randomized participants who took ≥1 study drug dose and were evaluable for this end point.

**Statistical analyses**

| Statistical analysis title                                                                                      | MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID |
|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. MF MDI 200 mcg BID pairwise comparison p-value |                                                |
| Comparison groups                                                                                               | MF/F MDI 200/10 mcg BID v MF MDI 200 mcg BID   |
| Number of subjects included in analysis                                                                         | 377                                            |
| Analysis specification                                                                                          | Pre-specified                                  |
| Analysis type                                                                                                   | superiority                                    |
| P-value                                                                                                         | = 0.063                                        |
| Method                                                                                                          | ANCOVA                                         |

| Statistical analysis title                                                                                    | MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID |
|---------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. F MDI 10 mcg BID pairwise comparison p-value |                                              |
| Comparison groups                                                                                             | MF/F MDI 200/10 mcg BID v F MDI 10 mcg BID   |
| Number of subjects included in analysis                                                                       | 385                                          |
| Analysis specification                                                                                        | Pre-specified                                |
| Analysis type                                                                                                 | superiority                                  |
| P-value                                                                                                       | < 0.001                                      |
| Method                                                                                                        | ANCOVA                                       |

|                                                                                                              |                                             |
|--------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b>                                                                            | MF/F MDI 200/10 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>MF/F MDI 200/10 mcg BID vs. Placebo MDI BID pairwise comparison p-value |                                             |
| Comparison groups                                                                                            | MF/F MDI 200/10 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                                      | 380                                         |
| Analysis specification                                                                                       | Pre-specified                               |
| Analysis type                                                                                                | superiority                                 |
| P-value                                                                                                      | < 0.001                                     |
| Method                                                                                                       | ANCOVA                                      |

|                                                                                                          |                                         |
|----------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>                                                                        | MF MDi 200 mcg BID vs. F MDI 10 mcg BID |
| Statistical analysis description:<br>MF MDi 200 mcg BID vs. F MDI 10 mcg BID pairwise comparison P-value |                                         |
| Comparison groups                                                                                        | MF MDI 200 mcg BID v F MDI 10 mcg BID   |
| Number of subjects included in analysis                                                                  | 390                                     |
| Analysis specification                                                                                   | Pre-specified                           |
| Analysis type                                                                                            | superiority                             |
| P-value                                                                                                  | < 0.001                                 |
| Method                                                                                                   | ANCOVA                                  |

|                                                                                                         |                                        |
|---------------------------------------------------------------------------------------------------------|----------------------------------------|
| <b>Statistical analysis title</b>                                                                       | MF MDi 200 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>MF MDi 200 mcg BID vs. Placebo MDI BID pairwise comparison P-value |                                        |
| Comparison groups                                                                                       | MF MDI 200 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                                 | 385                                    |
| Analysis specification                                                                                  | Pre-specified                          |
| Analysis type                                                                                           | superiority                            |
| P-value                                                                                                 | = 0.003                                |
| Method                                                                                                  | ANCOVA                                 |

|                                                                                                       |                                      |
|-------------------------------------------------------------------------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>                                                                     | F MDI 10 mcg BID vs. Placebo MDI BID |
| Statistical analysis description:<br>F MDI 10 mcg BID vs. Placebo MDI BID pairwise comparison P-value |                                      |
| Comparison groups                                                                                     | F MDI 10 mcg BID v Placebo MDI BID   |
| Number of subjects included in analysis                                                               | 393                                  |
| Analysis specification                                                                                | Pre-specified                        |
| Analysis type                                                                                         | superiority                          |
| P-value                                                                                               | = 0.601                              |
| Method                                                                                                | ANCOVA                               |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 26 weeks

|                 |            |
|-----------------|------------|
| 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 receive MF/F MDI 200/10 mcg BID for up to 26 weeks

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Placebo MDI BID |
|-----------------------|-----------------|

Reporting group description:

Participants receive placebo MDI BID for up to 26 weeks

|                       |                  |
|-----------------------|------------------|
| Reporting group title | F MDI 10 mcg BID |
|-----------------------|------------------|

Reporting group description:

Participants receive F MDI 10 mcg BID for up to 26 weeks

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | MF MDI 200 mcg BID |
|-----------------------|--------------------|

Reporting group description:

Participants receive MF MDI 200 mcg BID for up to 26 weeks

| Serious adverse events                                              | MF/F MDI 200/10 mcg BID | Placebo MDI BID | F MDI 10 mcg BID |
|---------------------------------------------------------------------|-------------------------|-----------------|------------------|
| Total subjects affected by serious adverse events                   |                         |                 |                  |
| subjects affected / exposed                                         | 5 / 191 (2.62%)         | 3 / 196 (1.53%) | 3 / 202 (1.49%)  |
| number of deaths (all causes)                                       | 1                       | 0               | 0                |
| number of deaths resulting from adverse events                      | 0                       | 0               | 0                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                 |                  |
| Uterine Leiomyosarcoma                                              |                         |                 |                  |
| subjects affected / exposed                                         | 1 / 191 (0.52%)         | 0 / 196 (0.00%) | 0 / 202 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 1                   | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 1                   | 0 / 0           | 0 / 0            |
| Malignant Melanoma                                                  |                         |                 |                  |
| subjects affected / exposed                                         | 0 / 191 (0.00%)         | 0 / 196 (0.00%) | 1 / 202 (0.50%)  |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0           | 0 / 0            |
| Injury, poisoning and procedural complications                      |                         |                 |                  |
| Humerus Fracture                                                    |                         |                 |                  |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 191 (0.00%) | 1 / 196 (0.51%) | 0 / 202 (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           |
| Surgical and medical procedures                 |                 |                 |                 |
| Spinal Decompression                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 191 (0.00%) | 1 / 196 (0.51%) | 0 / 202 (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           |
| Nervous system disorders                        |                 |                 |                 |
| Convulsion                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 191 (0.52%) | 0 / 196 (0.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoaesthesia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 191 (0.52%) | 0 / 196 (0.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Endometriosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 191 (0.00%) | 0 / 196 (0.00%) | 0 / 202 (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           |
| Vaginal Haemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 191 (0.52%) | 0 / 196 (0.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Asthma                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 191 (0.00%) | 0 / 196 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Dermatitis Atopic                               |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 191 (0.00%) | 1 / 196 (0.51%) | 0 / 202 (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           |
| <b>Eczema</b>                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 191 (0.52%) | 0 / 196 (0.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Infections and infestations</b>              |                 |                 |                 |
| <b>Gastroenteritis</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 191 (0.00%) | 0 / 196 (0.00%) | 0 / 202 (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           |
| <b>Viral Infection</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 191 (0.52%) | 0 / 196 (0.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Metabolism and nutrition disorders</b>       |                 |                 |                 |
| <b>Hyperglycaemia</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 191 (0.00%) | 0 / 196 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                                            |                       |  |  |
|----------------------------------------------------------------------------|-----------------------|--|--|
| <b>Serious adverse events</b>                                              | MF MDI 200 mcg<br>BID |  |  |
| Total subjects affected by serious adverse events                          |                       |  |  |
| subjects affected / exposed                                                | 3 / 192 (1.56%)       |  |  |
| number of deaths (all causes)                                              | 0                     |  |  |
| number of deaths resulting from adverse events                             | 0                     |  |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                       |  |  |
| <b>Uterine Leiomyosarcoma</b>                                              |                       |  |  |
| subjects affected / exposed                                                | 0 / 192 (0.00%)       |  |  |
| occurrences causally related to treatment / all                            | 0 / 0                 |  |  |
| deaths causally related to treatment / all                                 | 0 / 0                 |  |  |
| <b>Malignant Melanoma</b>                                                  |                       |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Humerus Fracture                                |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Surgical and medical procedures                 |                 |  |  |
| Spinal Decompression                            |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Convulsion                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypoaesthesia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Reproductive system and breast disorders        |                 |  |  |
| Endometriosis                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 192 (0.52%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vaginal Haemorrhage                             |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Asthma                                          |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 192 (0.52%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Dermatitis Atopic                               |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eczema                                          |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 192 (0.52%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Viral Infection                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hyperglycaemia                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | MF/F MDI 200/10 mcg BID | Placebo MDI BID   | F MDI 10 mcg BID  |
|-------------------------------------------------------|-------------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events |                         |                   |                   |
| subjects affected / exposed                           | 31 / 191 (16.23%)       | 30 / 196 (15.31%) | 29 / 202 (14.36%) |
| Nervous system disorders                              |                         |                   |                   |

|                                                                                                    |                        |                        |                        |
|----------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| Headache<br>subjects affected / exposed<br>occurrences (all)                                       | 9 / 191 (4.71%)<br>10  | 7 / 196 (3.57%)<br>10  | 6 / 202 (2.97%)<br>8   |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 12 / 191 (6.28%)<br>13 | 7 / 196 (3.57%)<br>8   | 13 / 202 (6.44%)<br>14 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)              | 11 / 191 (5.76%)<br>13 | 17 / 196 (8.67%)<br>17 | 12 / 202 (5.94%)<br>16 |

|                                                                                                    |                        |  |  |
|----------------------------------------------------------------------------------------------------|------------------------|--|--|
| <b>Non-serious adverse events</b>                                                                  | MF MDI 200 mcg<br>BID  |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed            | 35 / 192 (18.23%)      |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)           | 10 / 192 (5.21%)<br>17 |  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 15 / 192 (7.81%)<br>22 |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)              | 16 / 192 (8.33%)<br>16 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 22 October 2007 | Amendment 01: The main reasons for Amendment 01 were 1) to clarify that open-label run-in medication was to be dispensed at Visit 1, but that participants were NOT to start taking open-label MF MDI (run-in medication) until after the laboratory results were available and found to be clinically acceptable, 2) to clarify inclusion and exclusion criteria and 3) to modify the age of participants for countries such as Russia where minors are not permitted in clinical studies and therefore only adults (participants $\geq 18$ years of age) so as to reflect various Ethics Committees and Competent Authorities requirements. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported