



## Clinical trial results:

### MK-476 IV formulation Phase III Open Label Exploratory Comparative Study - Acute Exacerbations of Asthma -

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-004749-28 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 01 August 2007 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 13 June 2016 |
| First version publication date | 19 July 2015 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | MK-0476-334 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00442338 |
| WHO universal trial number (UTN)   | -           |

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)       | No  |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 01 August 2007 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 01 August 2007 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 01 August 2007 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The study estimates the efficacy and safety of MK-0476 and aminophylline intravenous (IV) administration in adult participants with acute asthma.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following additional measures defined for this individual study were in place for the protection of trial subjects: as needed administration of beta agonists, IV drip corticosteroids, and oxygen therapy during the treatment period.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 12 March 2007 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 91 |
| Worldwide total number of subjects   | 91        |
| EEA total number of subjects         | 0         |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 1  |
| Adults (18-64 years)                      | 57 |
| From 65 to 84 years                       | 33 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Phase III. Studied period: March 12, 2007 (date study drug was first administered to first participant) to August 1, 2007 (date study drug was last administered to last participant). Study was conducted at 31 clinical sites in Japan.

### Pre-assignment

Screening details:

Participants with acute exacerbation of bronchial asthma received standard treatments of inhaled  $\beta$ -agonist or oxygen inhalation to treat the acute exacerbations during the 60 minutes in the screening period before the study randomization. Additional inclusion and exclusion criteria applied.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Montelukast 7 mg |

Arm description:

Montelukast 7 mg IV administration

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | montelukast sodium    |
| Investigational medicinal product code |                       |
| Other name                             | MK-0476               |
| Pharmaceutical forms                   | Injection             |
| Routes of administration               | Intravenous bolus use |

Dosage and administration details:

Montelukast 7 mg single injection (IV bolus administration) over 2-3 minutes

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Montelukast 14 mg |
|------------------|-------------------|

Arm description:

Montelukast 14 mg IV administration

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | montelukast sodium    |
| Investigational medicinal product code |                       |
| Other name                             | MK-0476               |
| Pharmaceutical forms                   | Injection             |
| Routes of administration               | Intravenous bolus use |

Dosage and administration details:

Montelukast 14 mg single injection (IV bolus administration) over 5 minutes

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Aminophylline 250 mg |
|------------------|----------------------|

Arm description:

Aminophylline 250 mg IV drip administration

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | aminophylline hydrate            |
| Investigational medicinal product code |                                  |
| Other name                             | Kyophyllin® Injection 2.5%, FK05 |
| Pharmaceutical forms                   | Infusion                         |
| Routes of administration               | Intravenous drip use             |

Dosage and administration details:

Aminophylline 250 mg IV drip infusion over 60 minutes

| <b>Number of subjects in period 1</b> | Montelukast 7 mg | Montelukast 14 mg | Aminophylline 250 mg |
|---------------------------------------|------------------|-------------------|----------------------|
| Started                               | 30               | 30                | 31                   |
| Completed                             | 30               | 30                | 31                   |

## Baseline characteristics

### Reporting groups

|   |                      |
|---|----------------------|
| Reporting group title   | Montelukast 7 mg     |
| Reporting group description:<br>Montelukast 7 mg IV administration          |                      |
| Reporting group title   | Montelukast 14 mg    |
| Reporting group description:<br>Montelukast 14 mg IV administration         |                      |
| Reporting group title   | Aminophylline 250 mg |
| Reporting group description:<br>Aminophylline 250 mg IV drip administration |                      |

| Reporting group values  | Montelukast 7 mg | Montelukast 14 mg | Aminophylline 250 mg |
|---|------------------|-------------------|----------------------|
| Number of subjects  | 30               | 30                | 31                   |
| Age categorical<br>Units: Subjects  |                  |                   |                      |
| Adolescents (12-17 years)   | 0                | 1                 | 0                    |
| Adults (18-64 years)  | 21               | 16                | 20                   |
| From 65-84 years  | 9                | 13                | 11                   |
| Age Continuous<br>Units: years  |                  |                   |                      |
| arithmetic mean   | 56               | 56.7              | 55.4                 |
| standard deviation  | ± 12.3           | ± 15.2            | ± 14.5               |
| Gender, Male/Female<br>Units: participants  |                  |                   |                      |
| Female  | 22               | 24                | 16                   |
| Male  | 8                | 6                 | 15                   |
| Asthma Attack Severity based on<br>Asthma Prevention and Management<br>Guideline 2003, Japan  |                  |                   |                      |
| Mild (Peak Expiratory Flow >80%), Moderate (Peak Expiratory Flow: 60% ~ 80%), Severe (Peak Expiratory Flow <60%) or Serious (Peak Expiratory Flow: incapable measurement, cyanosis, head trip, disturbed consciousness, incontinence or asphyxia) |                  |                   |                      |
| Units: Subjects   |                  |                   |                      |
| Mild  | 21               | 18                | 26                   |
| Moderate  | 9                | 12                | 5                    |
| Severe  | 0                | 0                 | 0                    |
| Serious   | 0                | 0                 | 0                    |
| Baseline Forced Expiratory Volume in<br>One Second (FEV1)<br>Units: Liters  |                  |                   |                      |
| arithmetic mean   | 1.35             | 1.18              | 1.43                 |
| standard deviation  | ± 0.29           | ± 0.33            | ± 0.53               |
| Duration of Asthma<br>Units: Years  |                  |                   |                      |
| arithmetic mean   | 14.9             | 13.9              | 16.7                 |
| standard deviation  | ± 10.4           | ± 11.5            | ± 14.1               |
| Reporting group values  | Total            |                   |                      |

|   |    |  |  |
|---|----|--|--|
| Number of subjects  | 91 |  |  |
| Age categorical   |    |  |  |
| Units: Subjects   |    |  |  |
| Adolescents (12-17 years)   | 1  |  |  |
| Adults (18-64 years)  | 57 |  |  |
| From 65-84 years  | 33 |  |  |
| Age Continuous  |    |  |  |
| Units: years  |    |  |  |
| arithmetic mean   |    |  |  |
| standard deviation  | -  |  |  |
| Gender, Male/Female   |    |  |  |
| Units: participants   |    |  |  |
| Female  | 62 |  |  |
| Male  | 29 |  |  |
| Asthma Attack Severity based on<br>Asthma Prevention and Management<br>Guideline 2003, Japan  |    |  |  |
| Mild (Peak Expiratory Flow >80%), Moderate (Peak Expiratory Flow: 60% ~ 80%), Severe (Peak Expiratory Flow <60%) or Serious (Peak Expiratory Flow: incapable measurement, cyanosis, head trip, disturbed consciousness, incontinence or asphyxia) |    |  |  |
| Units: Subjects   |    |  |  |
| Mild  | 65 |  |  |
| Moderate  | 26 |  |  |
| Severe  | 0  |  |  |
| Serious   | 0  |  |  |
| Baseline Forced Expiratory Volume in<br>One Second (FEV1)   |    |  |  |
| Units: Liters   |    |  |  |
| arithmetic mean   |    |  |  |
| standard deviation  | -  |  |  |
| Duration of Asthma  |    |  |  |
| Units: Years  |    |  |  |
| arithmetic mean   |    |  |  |
| standard deviation  | -  |  |  |

## End points

### End points reporting groups

|   |                      |
|---|----------------------|
| Reporting group title   | Montelukast 7 mg     |
| Reporting group description:<br>Montelukast 7 mg IV administration          |                      |
| Reporting group title   | Montelukast 14 mg    |
| Reporting group description:<br>Montelukast 14 mg IV administration         |                      |
| Reporting group title   | Aminophylline 250 mg |
| Reporting group description:<br>Aminophylline 250 mg IV drip administration |                      |

### Primary: Change from Baseline in forced expiratory volume in one second (FEV1) within the first 60 minutes after administration

|   |  |
|---|--|
| End point title   | Change from Baseline in forced expiratory volume in one second (FEV1) within the first 60 minutes after administration |
| End point description:<br>The time weighted average change from Baseline in Forced Expiratory Volume in One Second (FEV1) over the first 60 minutes after study drug administration (average change FEV1 (0-60 min)). Baseline (pre-allocation) was the last measurement obtained during the screening period. Analysis was performed on data obtained from the Per Protocol Set, which is the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline and 60 minutes after study drug administration   |  |

| End point values                             | Montelukast 7 mg    | Montelukast 14 mg | Aminophylline 250 mg |  |
|--|---------------------|-------------------|----------------------|--|
| Subject group type                           | Reporting group     | Reporting group   | Reporting group      |  |
| Number of subjects analysed                  | 27 <sup>[1]</sup>   | 30                | 29 <sup>[2]</sup>    |  |
| Units: Liters                                |                     |                   |                      |  |
| least squares mean (confidence interval 95%) | 0.07 (0.02 to 0.12) | 0.05 (0 to 0.11)  | 0.06 (0.01 to 0.12)  |  |

Notes:

[1] - Participants receiving

[2] - 1 participant with no FEV1 data at 60 minutes was excluded from the analysis.

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Montelukast 7 mg vs. Aminophylline 250 mg |
| Statistical analysis description:<br>Treatment difference in change from Baseline in FEV1 within the first 60 minutes after study drug administration was assessed as the difference in the least square (LS) means of time weighted average change FEV1 (0-60 min) using an Analysis of Covariance (ANCOVA) model. The model included a factor for treatment and used the baseline FEV1 as a covariate. |   |
| Comparison groups  | Montelukast 7 mg v Aminophylline 250 mg   |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 56                     |
| Analysis specification                  | Post-hoc               |
| Analysis type                           | other                  |
| P-value                                 | = 0.871                |
| Method                                  | ANCOVA                 |
| Parameter estimate                      | Difference in LS Means |
| Point estimate                          | 0.01                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | -0.07                  |
| upper limit                             | 0.08                   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Montelukast 14 mg vs. Aminophylline 250 mg |
|-----------------------------------|--|

Statistical analysis description:

Treatment difference in change from Baseline in FEV1 within the first 60 minutes after study drug administration was assessed as the difference in the LS means of time weighted average change FEV1 (0-60 min) using an ANCOVA model. The model included a factor for treatment and used the baseline FEV1 as a covariate.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 14 mg v Aminophylline 250 mg |
| Number of subjects included in analysis | 59                                       |
| Analysis specification                  | Post-hoc                                 |
| Analysis type                           | other                                    |
| P-value                                 | = 0.794                                  |
| Method                                  | ANCOVA                                   |
| Parameter estimate                      | Difference in LS Means                   |
| Point estimate                          | -0.01                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.08                                    |
| upper limit                             | 0.06                                     |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Montelukast 7 mg vs. Montelukast 14 mg |
|-----------------------------------|--|

Statistical analysis description:

Treatment difference in change from Baseline in FEV1 within the first 60 minutes after study drug administration was assessed as the difference in the LS means of time weighted average change FEV1 (0-60 min) using an ANCOVA model. The model included a factor for treatment and used the baseline FEV1 as a covariate.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 14 mg v Aminophylline 250 mg |
| Number of subjects included in analysis | 59                                       |
| Analysis specification                  | Post-hoc                                 |
| Analysis type                           | other                                    |
| P-value                                 | = 0.675                                  |
| Method                                  | ANCOVA                                   |
| Parameter estimate                      | Difference in LS Means                   |
| Point estimate                          | 0.02                                     |



| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.06   |
| upper limit         | 0.09    |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Screening through post-trial visit (up to 14 days)

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |     |
|--------------------|-----|
| Dictionary version | 9.1 |
|--------------------|-----|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Montelukast 7 mg |
|-----------------------|------------------|

Reporting group description:

Montelukast 7 mg IV administration

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Montelukast 14 mg |
|-----------------------|-------------------|

Reporting group description:

Montelukast 14 mg IV administration

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Aminophylline 250 mg |
|-----------------------|----------------------|

Reporting group description:

Aminophylline 250 mg IV drip administration

| Serious adverse events                               | Montelukast 7 mg | Montelukast 14 mg | Aminophylline 250 mg |
|--|------------------|-------------------|----------------------|
| Total subjects affected by serious adverse events    |                  |                   |                      |
| subjects affected / exposed                          | 3 / 30 (10.00%)  | 0 / 30 (0.00%)    | 1 / 31 (3.23%)       |
| number of deaths (all causes)                        | 0                | 0                 | 0                    |
| number of deaths resulting from adverse events       |                  |                   |                      |
| Investigations                                       |                  |                   |                      |
| White blood cell count increased                     |                  |                   |                      |
| subjects affected / exposed                          | 1 / 30 (3.33%)   | 0 / 30 (0.00%)    | 0 / 31 (0.00%)       |
| occurrences causally related to treatment / all      | 1 / 1            | 0 / 0             | 0 / 0                |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0             | 0 / 0                |
| General disorders and administration site conditions |                  |                   |                      |
| Pyrexia  |                  |                   |                      |
| subjects affected / exposed                          | 1 / 30 (3.33%)   | 0 / 30 (0.00%)    | 0 / 31 (0.00%)       |
| occurrences causally related to treatment / all      | 1 / 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                     | 2 / 30 (6.67%) | 0 / 30 (0.00%) | 1 / 31 (3.23%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Montelukast 7 mg | Montelukast 14 mg | Aminophylline 250 mg |
|---|------------------|-------------------|----------------------|
| Total subjects affected by non-serious adverse events |                  |                   |                      |
| subjects affected / exposed                           | 5 / 30 (16.67%)  | 1 / 30 (3.33%)    | 3 / 31 (9.68%)       |
| Investigations  |                  |                   |                      |
| Glucose urine present                                 |                  |                   |                      |
| subjects affected / exposed                           | 2 / 30 (6.67%)   | 1 / 30 (3.33%)    | 1 / 31 (3.23%)       |
| occurrences (all)                                     | 2                | 1                 | 1                    |
| White blood cell count increased                      |                  |                   |                      |
| subjects affected / exposed                           | 0 / 30 (0.00%)   | 0 / 30 (0.00%)    | 2 / 31 (6.45%)       |
| occurrences (all)                                     | 0                | 0                 | 2                    |
| General disorders and administration site conditions  |                  |                   |                      |
| Oedema  |                  |                   |                      |
| subjects affected / exposed                           | 2 / 30 (6.67%)   | 0 / 30 (0.00%)    | 0 / 31 (0.00%)       |
| occurrences (all)                                     | 2                | 0                 | 0                    |
| Gastrointestinal disorders                            |                  |                   |                      |
| Diarrhoea   |                  |                   |                      |
| subjects affected / exposed                           | 2 / 30 (6.67%)   | 0 / 30 (0.00%)    | 0 / 31 (0.00%)       |
| occurrences (all)                                     | 2                | 0                 | 0                    |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported