



## Clinical trial results:

### A Multicenter, Randomised, Double Blind Study Comparing the Clinical Effects of Intravenous Montelukast With Placebo in Patients With Acute Asthma

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2004-000614-39 |
| Trial protocol           | IT DK          |
| Global end of trial date | 12 March 2007  |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v2 (current)  |
| This version publication date  | 20 May 2016   |
| First version publication date | 10 April 2015 |
| Version creation reason        |               |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 0476-288 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00092989 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Merck Sharpe & Dohme Corp.  |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033                                |
| Public contact               | Clinical Trials Disclosure, Merck Sharpe & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharpe & 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                       | 12 March 2007 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 12 March 2007 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 12 March 2007 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of montelukast (Singulair™) 7 mg, a leukotriene receptor antagonist, in the treatment of acute exacerbations of asthma when given as an intravenous (IV) bolus dose in addition to a standard care regimen consistent with the Global Initiative for Asthma (GINA) guideline recommendations. During a 60 minute screening period, change from baseline (BL) in lung function was quantified as forced expiratory volume in 1 second (FEV1) before and after the administration of standard care for acute asthma in an emergency department. The primary hypothesis was that in adult patients with acute asthma, the addition of montelukast IV 7 mg to standard therapy will cause a significant improvement in FEV1 within the first 60 minutes after administration (i.e., average change in FEV1 from preallocation baseline over the first 60 minutes after study drug administration) compared with placebo.

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 for this study were in place for the protection of trial participants: Rescue medication was available for participants that required rescue therapy within 3 hours following the end of study drug administration. Rescue therapy was defined as the administration of any of the following treatments within 30 minutes prior to end of study drug administration, or at least 10 minutes after end of study drug administration and within 3 hours following the end of study drug administration: systemic corticosteroids (prednisone/prednisolone), short-acting  $\beta$ -agonists (albuterol/salbutamol), short-acting anti-cholinergic drugs (ipratropium), magnesium.

Background therapy:

Upon entering the Screening Period (Period 1), standardized treatment for an acute severe asthma episode was initiated and continued throughout the Treatment Period (Period 2) for all participants. Standardized treatment could consist of: (1)  $\beta$ -agonist, (2) oxygen therapy, (3) inhaled ipratropium (optional), and 4) systemic corticosteroids (only administered following completion of study drug in Period 2).

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 06 July 2004 |
| 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 | Peru: 59         |
| Country: Number of subjects enrolled | Guatemala: 10    |
| Country: Number of subjects enrolled | South Africa: 22 |
| Country: Number of subjects enrolled | New Zealand: 5   |
| Country: Number of subjects enrolled | Mexico: 40       |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 5       |
| Country: Number of subjects enrolled | Colombia: 24       |
| Country: Number of subjects enrolled | United States: 318 |
| Country: Number of subjects enrolled | Brazil: 4          |
| Country: Number of subjects enrolled | Chile: 6           |
| Country: Number of subjects enrolled | India: 19          |
| Country: Number of subjects enrolled | Israel: 14         |
| Country: Number of subjects enrolled | Denmark: 1         |
| Country: Number of subjects enrolled | France: 28         |
| Country: Number of subjects enrolled | Italy: 28          |
| Worldwide total number of subjects   | 583                |
| EEA total number of subjects         | 57                 |

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)                 | 9   |
| Adults (18-64 years)                      | 529 |
| From 65 to 84 years                       | 45  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited from 34 sites in the United States and 28 sites in 15 countries.

### Pre-assignment

Screening details:

Screening began at participant arrival at the study site and consisted of the time between the start of urgent treatment (oxygen, short-acting  $\beta$ -agonist) and IV montelukast or placebo, not to exceed 60 minutes

### Pre-assignment period milestones

|                              |                     |
|------------------------------|---------------------|
| Number of subjects started   | 1147 <sup>[1]</sup> |
| Number of subjects completed | 583                 |

### Pre-assignment subject non-completion reasons

|                            |                                  |
|----------------------------|----------------------------------|
| Reason: Number of subjects | Participant ineligible: 545      |
| Reason: Number of subjects | Consent withdrawn by subject: 14 |
| Reason: Number of subjects | Protocol deviation: 5            |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number represents the number of eligible enrolled participants that were treated on study. 1147 participants were screened for inclusion.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Pre-allocation Evaluation and Treatment |
| Is this the baseline period? | No                                      |
| Allocation method            | Not applicable                          |
| Blinding used                | Not blinded                             |

### Arms

|           |   |
|-----------|---|
| Arm title | Pre-allocation Evaluation and Treatment |
|-----------|---|

Arm description:

Participants admitted to the study site because of an acute exacerbation of asthma entered the screening period (Period 1) and received standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting  $\beta$ -agonist, corticosteroid, ipratropium).

|   |                                    |
|---|------------------------------------|
| Arm type  | Pre-study Evaluation and Treatment |
| No investigational medicinal product assigned in this arm |                                    |

|                                       |   |
|---------------------------------------|---|
| <b>Number of subjects in period 1</b> | Pre-allocation Evaluation and Treatment |
| Started                               | 583                                     |
| Completed                             | 583                                     |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Active Treatment        |
| Is this the baseline period? | Yes <sup>[2]</sup>      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Investigator, Subject   |

## Arms

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

### Arm description:

During Period 2, randomised participants received IV montelukast 7 mg in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting  $\beta$ -agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of montelukast.

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | Montelukast sodium                         |
| Investigational medicinal product code |  |
| Other name                             | Singulair™                                 |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous bolus use                      |

### Dosage and administration details:

Participants received IV montelukast administered in one 7 mg dose after reconstitution of a vial containing montelukast sodium in a lyophilised powder form dissolved in 20 mL of a solution of 3.3% dextrose/0.3% sodium chloride and given as a manual bolus over a period of 2 to 5 minutes.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | Placebo + Standard Treatment |
|------------------|------------------------------|

### Arm description:

During Period 2, randomised participants received IV placebo for montelukast in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting  $\beta$ -agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of IV placebo.

|  |  |
|--|--|
| Arm type                               | Placebo                                    |
| Investigational medicinal product name | Placebo for montelukast                    |
| Investigational medicinal product code |  |
| Other name                             | Singulair™                                 |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous bolus use                      |

### Dosage and administration details:

Participants received matching placebo for montelukast supplied as a lyophilised powder in light-protected vials. Placebo powder was reconstituted in 20 mL of a solution of 3.3% dextrose/0.3% sodium chloride and given as a manual bolus infusion over 2 to 5 minutes.

### Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 was a screening period to determine eligible participants and to randomize participants. For the purpose of reporting baseline characteristics by reporting arm, Period 2 has been designated the baseline period.

| Number of subjects in period 2          | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment |
|---|---------------------------------------|------------------------------|
| Started                                 | 291                                   | 292                          |
| Completed                               | 288                                   | 285                          |
| Not completed                           | 3                                     | 7                            |
| Randomization error                     | 1                                     | -                            |
| Unable to do spirometry due to AEs      | -                                     | 1                            |
| Consent withdrawn by subject            | -                                     | 1                            |
| Unable to complete spirometry           | 1                                     | -                            |
| Adverse event, non-fatal                | -                                     | 1                            |
| Discontinued due to chest xray findings | 1                                     | -                            |
| Protocol deviation                      | -                                     | 1                            |
| Lack of efficacy                        | -                                     | 3                            |

### Period 3

|                              |                         |
|------------------------------|-------------------------|
| Period 3 title               | Post-study (14 Days)    |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | Montelukast 7 mg + Standard Treatment: Post-Study |

#### Arm description:

During the follow-up period, montelukast-treated participants received a telephone call approximately 14 days after the participant had completed Period 2 to review information on subsequent asthma-related healthcare contacts (doctor visits, emergency visits, and/or hospitalizations), asthma-related medication usage, impact on work, concomitant therapies, adverse experiences, and procedures that may have been performed within the 14 ± 3 days.

|   |  |
|---|--|
| Arm type  | Follow-up                                |
| No investigational medicinal product assigned in this arm |  |
| <b>Arm title</b>  | Placebo + Standard Treatment: Post-Study |

#### Arm description:

During the follow-up period, placebo-treated participants received a telephone call approximately 14 days after the participant had completed Period 2 to review information on subsequent asthma-related healthcare contacts (doctor visits, emergency visits, and/or hospitalizations), asthma-related medication usage, impact on work, concomitant therapies, adverse experiences, and procedures that may have been performed within the 14 ± 3 days.

|   |           |
|---|-----------|
| Arm type  | Follow-up |
| No investigational medicinal product assigned in this arm |           |

| Number of subjects in period 3                      | Montelukast 7 mg +<br>Standard<br>Treatment: Post-<br>Study | Placebo + Standard<br>Treatment: Post-<br>Study |
|---|---|---|
|   |   |   |
| Started   | 288   | 285   |
| Completed   | 291   | 292   |
|   |   |   |
| Joined  | 3   | 7   |
| Follow-up call, though did not<br>complete Period 2 | 3   | 7   |

## Baseline characteristics

### Reporting groups

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Montelukast 7 mg + Standard Treatment |
|-----------------------|---------------------------------------|

Reporting group description:

During Period 2, randomised participants received IV montelukast 7 mg in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting  $\beta$ -agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of montelukast.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Placebo + Standard Treatment |
|-----------------------|------------------------------|

Reporting group description:

During Period 2, randomised participants received IV placebo for montelukast in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting  $\beta$ -agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of IV placebo.

| Reporting group values             | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment | Total |
|------------------------------------|---------------------------------------|------------------------------|-------|
| Number of subjects                 | 291                                   | 292                          | 583   |
| Age categorical<br>Units: Subjects |                                       |                              |       |

|   |              |              |            |
|---|--------------|--------------|------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | 41.1<br>± 15 | 41<br>± 15.3 | -          |
| Gender categorical<br>Units: Subjects<br>Female<br>Male   | 153<br>138   | 175<br>117   | 328<br>255 |
| Baseline FEV1   |              |              |            |
| Baseline FEV1 was defined as last measurement obtained prior to the administration of study drug. Data were available for 287 in the Montelukast 7 mg group and 284 in the Placebo group. |              |              |            |
| Units: Liters<br>arithmetic mean<br>standard deviation  | 1.3<br>± 0.4 | 1.2<br>± 0.4 | -          |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Pre-allocation Evaluation and Treatment           |
| Reporting group description:<br>Participants admitted to the study site because of an acute exacerbation of asthma entered the screening period (Period 1) and received standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting $\beta$ -agonist, corticosteroid, ipratropium).   |   |
| Reporting group title  | Montelukast 7 mg + Standard Treatment             |
| Reporting group description:<br>During Period 2, randomised participants received IV montelukast 7 mg in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting $\beta$ -agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of montelukast.  |   |
| Reporting group title  | Placebo + Standard Treatment                      |
| Reporting group description:<br>During Period 2, randomised participants received IV placebo for montelukast in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting $\beta$ -agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of IV placebo.  |   |
| Reporting group title  | Montelukast 7 mg + Standard Treatment: Post-Study |
| Reporting group description:<br>During the follow-up period, montelukast-treated participants received a telephone call approximately 14 days after the participant had completed Period 2 to review information on subsequent asthma-related healthcare contacts (doctor visits, emergency visits, and/or hospitalizations), asthma-related medication usage, impact on work, concomitant therapies, adverse experiences, and procedures that may have been performed within the $14 \pm 3$ days. |   |
| Reporting group title  | Placebo + Standard Treatment: Post-Study          |
| Reporting group description:<br>During the follow-up period, placebo-treated participants received a telephone call approximately 14 days after the participant had completed Period 2 to review information on subsequent asthma-related healthcare contacts (doctor visits, emergency visits, and/or hospitalizations), asthma-related medication usage, impact on work, concomitant therapies, adverse experiences, and procedures that may have been performed within the $14 \pm 3$ days.     |   |

### Primary: Time-weighted Average Change from Baseline in FEV1 (0 to 60 minutes)

|   |  |
|---|--|
| End point title   | Time-weighted Average Change from Baseline in FEV1 (0 to 60 minutes) |
| End point description:<br>Time-weighted average change from baseline in FEV1 over the first 60 minutes after IV montelukast or placebo administration. Changes from baseline in FEV1 were computed at 10, 20, 40 and 60 minutes post study drug administration and then used to calculate a time-weighted average for 0-60 minutes, with the time interval between any measurement and the measurement prior to it being used as the weighting factor. The Full Analysis Set (FAS), comprised of all participants who started study drug and had efficacy measurements (FEV1) both at BL and at least one time point over the time interval considered, was used for this analysis. |  |
| End point type  | Primary  |
| End point timeframe:<br>0 minutes (baseline), 10, 20, 40, and 60 minutes after IV bolus infusion of montelukast 7 mg or placebo.  |  |

| End point values                             | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment |  |  |
|--|---------------------------------------|------------------------------|--|--|
| Subject group type                           | Reporting group                       | Reporting group              |  |  |
| Number of subjects analysed                  | 287 <sup>[1]</sup>                    | 284 <sup>[2]</sup>           |  |  |
| Units: Liters                                |                                       |                              |  |  |
| least squares mean (confidence interval 95%) | 0.32 (0.27 to 0.37)                   | 0.22 (0.17 to 0.27)          |  |  |

Notes:

[1] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[2] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

## Statistical analyses

| Statistical analysis title | Time-weighted Average $\Delta$ FEV1 (0-60 min) |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Time-weighted average change from baseline (BL) in FEV1, computed in the interval 0-60 minutes, was analysed using an analysis of covariance (ANCOVA) model with the baseline FEV1 as a covariate and including treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene (yes or no), and region (US or non-US) as factors. The ANCOVA model was used to estimate the least squares mean (LS mean) for treatment, between-treatment difference, and 95% CI.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment |
| Number of subjects included in analysis | 571  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | $\leq 0.001$ <sup>[3]</sup>  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS mean difference   |
| Point estimate                          | 0.1  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.04   |
| upper limit                             | 0.16   |

Notes:

[3] - P-value for LS mean difference between treatments, montelukast 7 mg versus placebo.

## Secondary: Percentage of Participants with Treatment Failure

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Treatment Failure |
|-----------------|---|

End point description:

The percentage of participants with treatment failure was summarized. Treatment failure was defined as: (1) participants that required hospitalization; or (2) participants for whom a decision to discharge home had not been reached by 3 hours following the end of study drug administration. The FAS was used for this analysis.

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

End point timeframe:

Up to  $\geq 3$  hours after IV manual bolus infusion of montelukast 7 mg or placebo.

| End point values                  | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment |  |  |
|-----------------------------------|---------------------------------------|------------------------------|--|--|
| Subject group type                | Reporting group                       | Reporting group              |  |  |
| Number of subjects analysed       | 287 <sup>[4]</sup>                    | 284 <sup>[5]</sup>           |  |  |
| Units: Percentage of Participants |                                       |                              |  |  |
| number (not applicable)           | 26.8                                  | 29.9                         |  |  |

Notes:

[4] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[5] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

## Statistical analyses

| Statistical analysis title | Percentage of Participants With Treatment Failure |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

A logistic regression model was used for analysis of the FAS population to compare the percentage of treatment failures between treatment groups. Factors in the model included treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene, and baseline FEV1 was used as a covariate. Descriptive statistics by treatment group provided by definition of treatment failure: participants requiring hospitalization or participants for whom decision to discharge home not reached by 3 hours.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment |
| Number of subjects included in analysis | 571  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority <sup>[6]</sup>   |
| P-value                                 | = 0.654 <sup>[7]</sup>   |
| Method                                  | Regression, Logistic   |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 0.92   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.63   |
| upper limit                             | 1.34   |

Notes:

[6] - Treatment differences were summarized by the odds ratio (OR) derived from the logistic regression model and the 95% CI.

[7] - Percentage of treatment failures in the IV montelukast 7 mg group compared to the placebo treatment group.

## Secondary: Time-weighted Average Change from Baseline in FEV1 (0 to 40 minutes)

|                 |  |
|-----------------|--|
| End point title | Time-weighted Average Change from Baseline in FEV1 (0 to 40 minutes) |
|-----------------|--|

End point description:

Time-weighted average change from baseline in FEV1 over the first 40 minutes after IV montelukast or placebo administration. Changes from baseline in FEV1 were computed at 10, 20, and 40 minutes post study drug administration and then used to calculate a time-weighted average for 0-40 minutes, with the time interval between any measurement and the measurement prior to it being used as the weighting factor. The FAS was used for this analysis.

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

End point timeframe:

0 minutes (BL), 10, 20, and 40 minutes after IV bolus infusion of montelukast 7 mg or placebo.

| End point values                             | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment |  |  |
|--|---------------------------------------|------------------------------|--|--|
| Subject group type                           | Reporting group                       | Reporting group              |  |  |
| Number of subjects analysed                  | 287 <sup>[8]</sup>                    | 283 <sup>[9]</sup>           |  |  |
| Units: Liters                                |                                       |                              |  |  |
| least squares mean (confidence interval 95%) | 0.28 (0.23 to 0.33)                   | 0.18 (0.13 to 0.23)          |  |  |

Notes:

[8] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[9] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

## Statistical analyses

| Statistical analysis title | Time-weighted Average ΔFEV1 (0-40 min) |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

The time weighted average change from baseline in FEV1, computed in the interval 0-40 minutes, was analysed with an ANCOVA model using the baseline FEV1 as a covariate and including treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene (yes/no), and region (US/Non-US) as factors. This ANCOVA model was used to estimate the least squares mean (LS-mean) for each treatment, between-treatment difference, and 95% CI.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment |
| Number of subjects included in analysis | 570  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | ≤ 0.001 <sup>[10]</sup>  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS mean difference   |
| Point estimate                          | 0.09   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.04   |
| upper limit                             | 0.15   |

Notes:

[10] - P-value for LS mean difference between treatments, montelukast 7 mg versus placebo.

## Secondary: Time-weighted Average Change From Baseline in FEV1 (0 to 20 minutes)

|                 |  |
|-----------------|--|
| End point title | Time-weighted Average Change From Baseline in FEV1 (0 to 20 minutes) |
|-----------------|--|

End point description:

Time-weighted average change from baseline in FEV1 over the first 20 minutes after IV montelukast or placebo administration. Changes from baseline in FEV1 were computed at 10 and 20 minutes post study drug administration and then used to calculate a time-weighted average for 0-20 minutes, with the time interval between any measurement and the measurement prior to it being used as the weighting factor. The FAS was used for this analysis.

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

End point timeframe:

0 minutes (BL), 10, and 20 minutes after IV bolus infusion of montelukast 7 mg or placebo.

| End point values                             | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment |  |  |
|--|---------------------------------------|------------------------------|--|--|
| Subject group type                           | Reporting group                       | Reporting group              |  |  |
| Number of subjects analysed                  | 287 <sup>[11]</sup>                   | 282 <sup>[12]</sup>          |  |  |
| Units: Liters                                |                                       |                              |  |  |
| least squares mean (confidence interval 95%) | 0.23 (0.19 to 0.28)                   | 0.15 (0.1 to 0.2)            |  |  |

Notes:

[11] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[12] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

## Statistical analyses

| Statistical analysis title | Time-weighted Average $\Delta$ FEV1 (0-20 min) |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

The time weighted average change from baseline in FEV1, computed in the interval 0-20 minutes, was analysed with an ANCOVA model using the baseline FEV1 as a covariate and including treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene (yes/no), and region (US/Non-US) as factors. This ANCOVA model was used to estimate the least squares mean (LS-mean) for each treatment, between-treatment difference, and 95% CI.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment |
| Number of subjects included in analysis | 569  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.002 <sup>[13]</sup>  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS mean difference   |
| Point estimate                          | 0.09   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.03   |
| upper limit                             | 0.14   |

Notes:

[13] - P-value for LS mean difference between treatments, i.e., montelukast 7 mg versus placebo.

## Secondary: Average Change from Baseline in FEV1 at 10 minutes

|                 |  |
|-----------------|--|
| End point title | Average Change from Baseline in FEV1 at 10 minutes |
|-----------------|--|

End point description:

Average change from baseline in FEV1 at 10 minutes after IV montelukast or placebo. The FAS was used for this analysis.

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

End point timeframe:

0 minutes (baseline), 10 minutes after IV manual bolus infusion of montelukast 7 mg or placebo.

| End point values                             | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment |  |  |
|--|---------------------------------------|------------------------------|--|--|
| Subject group type                           | Reporting group                       | Reporting group              |  |  |
| Number of subjects analysed                  | 269 <sup>[14]</sup>                   | 260 <sup>[15]</sup>          |  |  |
| Units: Liters                                |                                       |                              |  |  |
| least squares mean (confidence interval 95%) | 0.2 (0.15 to 0.26)                    | 0.12 (0.06 to 0.17)          |  |  |

Notes:

[14] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[15] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

## Statistical analyses

| Statistical analysis title | Average $\Delta$ FEV1 at 10 min |
|----------------------------|---------------------------------|
|----------------------------|---------------------------------|

Statistical analysis description:

The average change from baseline in FEV1, computed at 10 minutes, was analysed with an ANCOVA model using the baseline FEV1 as a covariate and including treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene (yes/no), and region (US/Non-US) as factors. This ANCOVA model was used to estimate the least squares mean (LS-mean) for each treatment, between treatment difference, and 95% CI.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment |
| Number of subjects included in analysis | 529  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.008 <sup>[16]</sup>  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS mean difference   |
| Point estimate                          | 0.08   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.02   |
| upper limit                             | 0.15   |

Notes:

[16] - P-value for LS mean difference between treatments, i.e., montelukast 7 mg versus placebo.

## Secondary: Total Dose of $\beta$ -agonist Administered Within 3 Hours

|                 |  |
|-----------------|--|
| End point title | Total Dose of $\beta$ -agonist Administered Within 3 Hours |
|-----------------|--|

End point description:

Total dose of  $\beta$ -agonist in mg administered per participant within 3 hours following end of study drug administration or placebo. Participants hospitalised prior to 3 hours post IV montelukast or placebo administration were assigned the largest total dose of  $\beta$ -agonist observed over all randomised participants plus 1 mg, or 5 mg plus 1 mg, whichever is larger.

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

End point timeframe:

Up to 3 hours following end of IV manual bolus infusion of montelukast 7 mg or placebo.

| End point values                      | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment |  |  |
|---------------------------------------|---------------------------------------|------------------------------|--|--|
| Subject group type                    | Reporting group                       | Reporting group              |  |  |
| Number of subjects analysed           | 287 <sup>[17]</sup>                   | 284 <sup>[18]</sup>          |  |  |
| Units: mg                             |                                       |                              |  |  |
| median (inter-quartile range (Q1-Q3)) | 5 (1 to 10)                           | 5 (0.9 to 10)                |  |  |

Notes:

[17] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

[18] - Participants starting study drug with FEV1 both at BL and at least 1 time point over interval (FAS).

## Statistical analyses

| Statistical analysis title | Total Dose of $\beta$ -Agonist |
|----------------------------|--------------------------------|
|----------------------------|--------------------------------|

Statistical analysis description:

A non-parametric ANCOVA model based on Tukey's normalised ranks was used with factors for treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene, region, and rank of BL FEV1 as covariate. Total dose of  $\beta$ -agonist administered per participant over a period of 3 hours following end of study drug administration was compared between treatment groups. Within-treatment effect was described using medians. Difference between medians were computed by the Hodges-Lehmann estimation.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment |
| Number of subjects included in analysis | 571  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other <sup>[19]</sup>  |
| P-value                                 | = 0.952 <sup>[20]</sup>  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Median difference (final values)                                     |
| Point estimate                          | 0  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0  |
| upper limit                             | 0  |

Notes:

[19] - Distribution-free confidence interval was based on the rank-sum test.

[20] - P-value for comparison between treatment groups, IV montelukast 7 mg versus placebo treatment.

## Secondary: Number of Doses of $\beta$ -agonist Administered Within 3 Hours

|                 |   |
|-----------------|---|
| End point title | Number of Doses of $\beta$ -agonist Administered Within 3 Hours |
|-----------------|---|

End point description:

Number of times a dose of a  $\beta$ -agonist was administered per participant within 3 hours following end of study drug or placebo administration. Participants hospitalised prior to 3 hours post study drug or placebo administration were assigned the largest number of  $\beta$ -agonist doses administered as observed over all randomised patients.

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

End point timeframe:

Up to 3 hours after IV manual bolus infusion of montelukast 7 mg or placebo.

| End point values                      | Montelukast 7 mg + Standard Treatment | Placebo + Standard Treatment |  |  |
|---------------------------------------|---------------------------------------|------------------------------|--|--|
| Subject group type                    | Reporting group                       | Reporting group              |  |  |
| Number of subjects analysed           | 287                                   | 284                          |  |  |
| Units: Doses                          |                                       |                              |  |  |
| median (inter-quartile range (Q1-Q3)) | 2 (1 to 3)                            | 2 (1 to 4)                   |  |  |

## Statistical analyses

| Statistical analysis title | Number of Doses of $\beta$ -agonist |
|----------------------------|-------------------------------------|
|----------------------------|-------------------------------------|

Statistical analysis description:

A non-parametric ANCOVA model based on Tukey's normalised ranks was used with factors for treatment, prior therapy with systemic corticosteroids and/or anti-leukotriene, region, and rank of BL FEV1 as covariate. Number of doses of  $\beta$ -agonist administered per participant over a period of 3 hours following end of study drug administration was compared between treatment groups. Within-treatment effect was described using medians. Difference of medians was computed by the Hodges-Lehmann estimation.

|   |  |
|---|--|
| Comparison groups                       | Montelukast 7 mg + Standard Treatment v Placebo + Standard Treatment |
| Number of subjects included in analysis | 571  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other <sup>[21]</sup>  |
| P-value                                 | = 0.265 <sup>[22]</sup>  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | Median difference (final values)                                     |
| Point estimate                          | 0  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0  |
| upper limit                             | 0  |

Notes:

[21] - Distribution-free confidence interval was based on the rank-sum test.

[22] - P-value for comparison between treatment groups, IV montelukast 7 mg versus placebo treatment.

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

During the treatment period after IV montelukast or placebo administration until permanent discontinuation (end of Period 2) plus 14 days (Post-study, Period 3).

Adverse event reporting additional description:

All randomised patients who started study drug were included in the All-Participants-as-Treated (APaT) set for the safety analyses. The participant's treatment group was determined by the actual treatment received.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Placebo + Standard Treatment |
|-----------------------|------------------------------|

Reporting group description:

During Period 2, randomised participants received IV placebo for montelukast in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting  $\beta$ -agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of IV placebo.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Montelukast 7 mg + Standard Treatment |
|-----------------------|---------------------------------------|

Reporting group description:

During Period 2, randomised participants received IV montelukast 7 mg in addition to a standard therapy regimen recommended by international guidelines for an acute severe asthma episode (e.g. oxygen, short-acting  $\beta$ -agonist, corticosteroid, ipratropium). Time-weighted change in FEV1 as a measure of lung function was determined for up to 120 minutes post-infusion of montelukast.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No nonserious adverse events reaching the cut-off of >5% on at least one treatment arm were reported.

| Serious adverse events                            | Placebo + Standard Treatment | Montelukast 7 mg + Standard Treatment |  |
|---|------------------------------|---------------------------------------|--|
| Total subjects affected by serious adverse events |                              |                                       |  |
| subjects affected / exposed                       | 26 / 292 (8.90%)             | 28 / 291 (9.62%)                      |  |
| number of deaths (all causes)                     | 1                            | 0                                     |  |
| number of deaths resulting from adverse events    | 0                            | 0                                     |  |
| Injury, poisoning and procedural complications    |                              |                                       |  |
| Drug Toxicity                                     |                              |                                       |  |
| subjects affected / exposed                       | 1 / 292 (0.34%)              | 0 / 291 (0.00%)                       |  |
| occurrences causally related to treatment / all   | 0 / 1                        | 0 / 0                                 |  |
| deaths causally related to treatment / all        | 0 / 1                        | 0 / 0                                 |  |
| Nervous system disorders                          |                              |                                       |  |
| Transient ischaemic attack                        |                              |                                       |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 292 (0.00%)  | 1 / 291 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Cholecystitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 292 (0.34%)  | 0 / 291 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Asthma  |                  |                  |  |
| subjects affected / exposed                     | 23 / 292 (7.88%) | 23 / 291 (7.90%) |  |
| occurrences causally related to treatment / all | 1 / 24           | 0 / 24           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic obstructive pulmonary disease           |                  |                  |  |
| subjects affected / exposed                     | 0 / 292 (0.00%)  | 2 / 291 (0.69%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspnoea  |                  |                  |  |
| subjects affected / exposed                     | 0 / 292 (0.00%)  | 1 / 291 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Status asthmaticus                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 292 (0.34%)  | 0 / 291 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Varicella                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 292 (0.34%)  | 0 / 291 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Hyperglycaemia                                  |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 292 (0.00%) | 1 / 291 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | Placebo + Standard Treatment | Montelukast 7 mg + Standard Treatment |  |
|---|------------------------------|---------------------------------------|--|
| Total subjects affected by non-serious adverse events |                              |                                       |  |
| subjects affected / exposed                           | 0 / 292 (0.00%)              | 0 / 291 (0.00%)                       |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 22 March 2005 | Amendment 01: Primary reasons for the amendment were to incorporate revisions to the inclusion and exclusion criteria, add language that removes the requirement to report hospitalisation due to worsening asthma (which is also a study endpoint) as a serious adverse experience, and include an updated montelukast sodium product circular that includes new in vitro data regarding CYP2C8. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported