# Clinical trial results:
# A Double-Blind, Placebo-Controlled, Multicenter, Crossover Study to Evaluate the Effects of a Single Oral Dose of Montelukast, Compared with Placebo, on Exercise-Induced Bronchoconstriction (EIB) in Pediatric Patients aged 4 to 14 years

## Summary

| | |
|---|---|
| EudraCT number | 2007-004879-19 |
| Trial protocol | EE |
| Global end of trial date | 26 March 2010 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 March 2016 |
| First version publication date | 08 July 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 0476-377 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00534976 |
| 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., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 26 March 2010 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 March 2010 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 March 2010 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This study will see if there is a change in breathing after exercising when the child receives study drug (montelukast or placebo). Breathing will be measured by a spirometer before exercising and measured again several times after exercising.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.
The following additional measure defined for this individual study was in place for the protection of trial subjects: rescue with inhaled short-acting beta-agonist.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 26 January 2008 |
| 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 | Colombia: 9 |
| Country: Number of subjects enrolled | Costa Rica: 1 |
| Country: Number of subjects enrolled | Estonia: 23 |
| Country: Number of subjects enrolled | United States: 33 |
| Worldwide total number of subjects | 66 |
| EEA total number of subjects | 23 |

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) | 33 |
| Adolescents (12-17 years) | 33 |

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

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Of the 364 participants screened for inclusion, 298 participants were excluded during screening and were not randomized. The remaining 66 participants met inclusion criteria and were randomly allocated to one of the two treatment sequences.

### Period 1

| | |
|---|---|
| Period 1 title | Period 1: Placebo Run-in |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Montelukast/ Placebo |

Arm description:

In Period 1 (screening period/ placebo run-in), participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one montelukast 4-mg chewable tablet (single dose). Period 3 was the crossover to one matching placebo 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one montelukast 5-mg chewable tablet (single dose) in Period 2, crossing over to one matching placebo 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Chewable tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants 4-5 years: matching placebo to 4 mg montelukast chewable tablet daily; Participants 6-14 years: matching placebo to 5 mg montelukast chewable tablet daily

| | |
|---|---|
| **Arm title** | Placebo/ Montelukast |

Arm description:

In Period 1 (screening period/ placebo run-in), participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one placebo 4-mg chewable tablet (single dose). Period 3 was the crossover to one montelukast 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one placebo 5-mg chewable tablet (single dose) in Period 2, crossing over to one montelukast 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Chewable tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants 4-5 years: matching placebo to 4 mg montelukast chewable tablet daily; Participants 6-14 years: matching placebo to 5 mg montelukast chewable tablet daily

| Number of subjects in period 1 | Montelukast/ Placebo | Placebo/ Montelukast |
|---|---|---|
| Started | 33 | 33 |
| Completed | 33 | 33 |

## Period 2

| | |
|---|---|
| Period 2 title | Period 2: Day 1 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Montelukast/ Placebo |

Arm description:

In Period 1 (screening period/ placebo run-in), participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one montelukast 4-mg chewable tablet (single dose). Period 3 was the crossover to one matching placebo 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one montelukast 5-mg chewable tablet (single dose) in Period 2, crossing over to one matching placebo 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Montelukast sodium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Chewable tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants 4-5 years: single dose of 4 mg montelukast chewable tablet on Day 1; Participants 6-14 years: single dose of 5 mg montelukast chewable tablet on Day 1

| | |
|---|---|
| **Arm title** | Placebo/ Montelukast |

Arm description:

In Period 1 (screening period/ placebo run-in) participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one placebo 4-mg chewable tablet (single dose). Period 3 was the crossover to one montelukast 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one placebo 5-mg chewable tablet (single dose) in Period 2, crossing over to one montelukast 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Chewable tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants 4-5 years: single dose of matching placebo to 4 mg montelukast chewable tablet daily on Day 1; Participants 6-14 years: single dose of matching placebo to 5 mg montelukast chewable tablet on Day 1

| **Number of subjects in period 2** | Montelukast/ Placebo | Placebo/ Montelukast |
|---|---|---|
| Started | 33 | 33 |
| Completed | 33 | 32 |
| Not completed | 0 | 1 |
| Protocol deviation | - | 1 |

**Period 3**

| | |
|---|---|
| Period 3 title | Period 3: Day 5 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

**Arms**

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Montelukast/ Placebo |

Arm description:

In Period 1 (screening period/ placebo run-in) participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one montelukast 4-mg chewable tablet (single dose). Period 3 was the crossover to one matching placebo 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one montelukast 5-mg chewable tablet (single dose) in Period 2, crossing over to one matching placebo 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Chewable tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants 4-5 years: single dose of matching placebo to 4 mg montelukast chewable tablet on Day 5; Participants 6-14 years: single dose of matching placebo to 5 mg montelukast chewable tablet on Day 5

| | |
|---|---|
| **Arm title** | Placebo/ Montelukast |

Arm description:

In Period 1 (screening period/ placebo run-in) participants received a single-blind dose of matching-

image placebo. In Period 2, participants 4-5 years of age were randomized to receive one placebo 4-mg chewable tablet (single dose). Period 3 was the crossover to one montelukast 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one placebo 5-mg chewable tablet (single dose) in Period 2, crossing over to one montelukast 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Montelukast sodium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Chewable tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants 4-5 years: single dose of 4 mg montelukast chewable tablet on Day 5; Participants 6-14 years: single dose of 5 mg montelukast chewable tablet on Day 5

| **Number of subjects in period 3** | Montelukast/ Placebo | Placebo/ Montelukast |
|---|---|---|
| Started | 33 | 32 |
| Completed | 31 | 32 |
| Not completed | 2 | 0 |
| Physician decision | 1 | - |
| Consent withdrawn by subject | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Montelukast/ Placebo |

Reporting group description:

In Period 1 (screening period/ placebo run-in), participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one montelukast 4-mg chewable tablet (single dose). Period 3 was the crossover to one matching placebo 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one montelukast 5-mg chewable tablet (single dose) in Period 2, crossing over to one matching placebo 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| Reporting group title | Placebo/ Montelukast |
|---|---|

Reporting group description:

In Period 1 (screening period/ placebo run-in), participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one placebo 4-mg chewable tablet (single dose). Period 3 was the crossover to one montelukast 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one placebo 5-mg chewable tablet (single dose) in Period 2, crossing over to one montelukast 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| Reporting group values | Montelukast/ Placebo | Placebo/ Montelukast | Total |
|---|---|---|---|
| Number of subjects | 33 | 33 | 66 |
| Age categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 10.9 | 11.5 | |
| standard deviation | ± 2.3 | ± 1.8 | - |
| Gender, Male/Female<br>Units: participants | | | |
| Female | 14 | 15 | 29 |
| Male | 19 | 18 | 37 |

## End points

### End points reporting groups

| Reporting group title | Montelukast/ Placebo |
|---|---|

Reporting group description:

In Period 1 (screening period/ placebo run-in), participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one montelukast 4-mg chewable tablet (single dose). Period 3 was the crossover to one matching placebo 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one montelukast 5-mg chewable tablet (single dose) in Period 2, crossing over to one matching placebo 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| Reporting group title | Placebo/ Montelukast |
|---|---|

Reporting group description:

In Period 1 (screening period/ placebo run-in), participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one placebo 4-mg chewable tablet (single dose). Period 3 was the crossover to one montelukast 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one placebo 5-mg chewable tablet (single dose) in Period 2, crossing over to one montelukast 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| Reporting group title | Montelukast/ Placebo |
|---|---|

Reporting group description:

In Period 1 (screening period/ placebo run-in), participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one montelukast 4-mg chewable tablet (single dose). Period 3 was the crossover to one matching placebo 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one montelukast 5-mg chewable tablet (single dose) in Period 2, crossing over to one matching placebo 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| Reporting group title | Placebo/ Montelukast |
|---|---|

Reporting group description:

In Period 1 (screening period/ placebo run-in) participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one placebo 4-mg chewable tablet (single dose). Period 3 was the crossover to one montelukast 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one placebo 5-mg chewable tablet (single dose) in Period 2, crossing over to one montelukast 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| Reporting group title | Montelukast/ Placebo |
|---|---|

Reporting group description:

In Period 1 (screening period/ placebo run-in) participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one montelukast 4-mg chewable tablet (single dose). Period 3 was the crossover to one matching placebo 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one montelukast 5-mg chewable tablet (single dose) in Period 2, crossing over to one matching placebo 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| Reporting group title | Placebo/ Montelukast |
|---|---|

Reporting group description:

In Period 1 (screening period/ placebo run-in) participants received a single-blind dose of matching-image placebo. In Period 2, participants 4-5 years of age were randomized to receive one placebo 4-mg chewable tablet (single dose). Period 3 was the crossover to one montelukast 4-mg chewable tablet (single dose) after a 3- to 7-day washout period. No participants 4-5 years of age were randomized, so the 4-mg doses were not dispensed. Participants 6-14 years of age were randomized to receive one placebo 5-mg chewable tablet (single dose) in Period 2, crossing over to one montelukast 5-mg chewable tablet (single dose) in Period 3 after a 3- to 7-day washout period.

| Subject analysis set title | Montelukast |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Completers analysis population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

| Subject analysis set title | Placebo |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Completers analysis population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

| Subject analysis set title | Montelukast |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Completers analysis population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

| Subject analysis set title | Placebo |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Completers analysis population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

## Primary: Maximum Percent Fall in FEV1 After Exercise Challenge at 2 Hours Postdose

| End point title | Maximum Percent Fall in FEV1 After Exercise Challenge at 2 Hours Postdose |
|---|---|

End point description:

Maximum Percent Fall in FEV1 was defined as the % change from pre-exercise baseline FEV1 to the lowest FEV1 within 60 mins (minutes) after exercise. Spirometry measurements were taken 5 mins prior to each exercise challenge and immediately, 5, 10, 15, 30, 45, & 60 mins after each exercise challenge. The 2-hour exercise challenges occurred 2 hours after the witnessed dose of study medication. The calculation used to produce the results was [100*(1-(X/Y))] where X= the lowest FEV1 within 60 mins after exercise & Y= pre-exercise baseline FEV1. Smaller values mean greater response to therapy. The analysis of efficacy data was carried out using a completers analysis population. This population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

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

End point timeframe:

Pre-exercise baseline and 0-60 minutes after the exercise challenge performed 2 hours post-dose

| **End point values** | Montelukast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 64 | 64 | | |
| Units: Percent fall in FEV1 | | | | |
| arithmetic mean (standard deviation) | 15.35 (± 9.47) | 20 (± 15.75) | | |

## Statistical analyses

| Statistical analysis title | Comparison between montelukast vs. placebo |
|---|---|

Statistical analysis description:

There were a total of 64 participants included in this analysis (cross-over design).

| | |
|---|---|
| Comparison groups | Montelukast v Placebo |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 |
| Method | ANOVA |
| Parameter estimate | Difference in least squares mean |
| Point estimate | -4.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.55 |
| upper limit | -0.75 |

## Secondary: Maximum percent fall in FEV1 after exercise challenge at 24 hours post-dose

| End point title | Maximum percent fall in FEV1 after exercise challenge at 24 hours post-dose |
|---|---|

End point description:

Maximum Percent Fall in FEV1 was defined as the % change from pre-exercise baseline FEV1 to the lowest FEV1 within 60 mins after exercise. Spirometry measurements were taken 5 mins prior to each exercise challenge and immediately, 5, 10, 15, 30, 45, & 60 mins after each exercise challenge. The 24-hour exercise challenges occurred 20-24 hours after the witnessed dose of study medication. The calculation used to produce the resulted results was [100*(1-(X/Y))] where X= the lowest FEV1 within 60 mins after exercise & Y= pre-exercise baseline FEV1. Smaller values mean greater response to therapy. The analysis of efficacy data was carried out using a completers analysis population. This population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

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

End point timeframe:

Pre-exercise baseline and 0-60 minutes after the exercise challenge performed 24 hours post-dose

| End point values | Montelukast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 62 | 62 | | |
| Units: percent fall in FEV1 | | | | |
| arithmetic mean (standard deviation) | 12.96 (± 10.38) | 17.22 (± 12.06) | | |

## Statistical analyses

| Statistical analysis title | Comparison between montelukast vs. placebo |
|---|---|

Statistical analysis description:

There were a total of 62 participants included in this analysis (cross-over design).

| | |
|---|---|
| Comparison groups | Montelukast v Placebo |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.005 |
| Method | ANOVA |
| Parameter estimate | Difference in least squares mean |
| Point estimate | -4.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.31 |
| upper limit | -1.34 |

## Secondary: Area Under the Curve for FEV1 percent fall from pre-exercise baseline to 60 minutes following exercise challenge (AUC0-60 min) at 2 hours post-dose

| End point title | Area Under the Curve for FEV1 percent fall from pre-exercise baseline to 60 minutes following exercise challenge (AUC0-60 min) at 2 hours post-dose |
|---|---|

End point description:

AUC0-60min was defined as the Area Under the Curve for FEV1 percent change from pre-exercise baseline to the 60 mins following exercise challenge. The area was computed by applying the trapezoidal rule, and including only the area below the pre-exercise baseline. If a participant received β-agonist during the 60 mins after the exercise challenge, the FEV1 measurements obtained after β-agonist administration were excluded and the last pre-rescue FEV1 measurement was carried forward to the 60 mins time point in the calculation of the AUC0-60 min. Smaller values mean greater response to therapy. The analysis of efficacy data was carried out using a completers analysis population. This population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

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

End point timeframe:

Pre-exercise baseline to 60 minutes after the exercise challenge performed 2 hours post-dose

| End point values | Montelukast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 64 | 64 | | |
| Units: percent fall * minute | | | | |
| arithmetic mean (standard deviation) | 294.5 (± 278.46) | 415.37 (± 375.94) | | |

## Statistical analyses

| Statistical analysis title | Comparison between montelukast vs. placebo |
|---|---|

Statistical analysis description:

There were a total of 64 participants included in this analysis (cross-over design).

| | |
|---|---|
| Comparison groups | Montelukast v Placebo |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.022 |
| Method | ANOVA |
| Parameter estimate | Difference in least squares mean |
| Point estimate | -120.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -223.77 |
| upper limit | -17.95 |

## Secondary: Area Under the Curve for FEV1 percent fall from pre-exercise baseline to 60 minutes following exercise challenge (AUC0-60 min) at 24 hours post-dose

| End point title | Area Under the Curve for FEV1 percent fall from pre-exercise baseline to 60 minutes following exercise challenge (AUC0-60 min) at 24 hours post-dose |
|---|---|

End point description:

AUC0-60min was defined as the Area Under the Curve for FEV1 percent change from pre-exercise baseline to the 60 mins following exercise challenge. The area was computed by applying the trapezoidal rule, and including only the area below the pre-exercise baseline. If a participant received β-agonist during the 60 mins after the exercise challenge, the FEV1 measurements obtained after β-agonist administration were excluded and the last pre-rescue FEV1 measurement was carried forward to the 60 mins time point in the calculation of the AUC0-60 min. Smaller values mean greater response to therapy. The analysis of efficacy data was carried out using a completers analysis population. This population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

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

End point timeframe:

Pre-exercise baseline to 60 minutes after the exercise challenge performed 24 hours post-dose

| End point values | Montelukast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 62 | 62 | | |
| Units: percent fall * minute | | | | |
| arithmetic mean (standard deviation) | 229.19 (± 233.93) | 349.59 (± 315.29) | | |

## Statistical analyses

| **Statistical analysis title** | Comparison between montelukast vs. placebo |
|---|---|

Statistical analysis description:

There were a total of 62 participants included in this analysis (cross-over design).

| | |
|---|---|
| Comparison groups | Montelukast v Placebo |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.013 |
| Method | ANOVA |
| Parameter estimate | Difference in least squares mean |
| Point estimate | -122.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -218.36 |
| upper limit | -27.29 |

## Secondary: Time to recovery from Maximum Percent Fall in FEV1 at 2 hours post-dose

| End point title | Time to recovery from Maximum Percent Fall in FEV1 at 2 hours post-dose |
|---|---|

End point description:

This endpoint was defined as the duration between the time at which the maximum percent fall in FEV1 occurred & the time when the percent fall in FEV1 returned to within 5% of the pre-exercise baseline for the first time. Spirometry measurements were taken 5 mins prior to each exercise challenge & immediately, 5, 10, 15, 30, 45, & 60 mins after each exercise challenge. If participant had not returned to within 5% of the pre-exercise FEV1 value by 60 mins, then measurements were obtained at 75 & 90 mins. The 2-hour exercise challenges occurred 2 hours after the witnessed dose of medication. The analysis of efficacy data was carried out using a completers analysis population. This population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

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

End point timeframe:

0-60 minutes and 0-90 minutes after the exercise challenge at 2 hours postdose

| **End point values** | Montelukast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 64 | 64 | | |
| Units: Minutes | | | | |
| arithmetic mean (standard deviation) | 16.21 (± 22.01) | 24.48 (± 27.91) | | |

## Statistical analyses

| **Statistical analysis title** | Comparison between montelukast vs. placebo |
|---|---|
| Statistical analysis description: | |
| There were a total of 64 participants included in this analysis (cross-over design). | |
| Comparison groups | Montelukast v Placebo |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.064 |
| Method | ANOVA |
| Parameter estimate | Difference in least squares mean |
| Point estimate | -8.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.04 |
| upper limit | 0.51 |

## Secondary: Time to recovery from maximum percent fall in FEV1 at 24 hours post-dose

| End point title | Time to recovery from maximum percent fall in FEV1 at 24 hours post-dose |
|---|---|

End point description:

This endpoint was defined as the duration between the time at which the maximum percent fall in FEV1 occurred & the time when the percent fall in FEV1 returned to within 5% of the pre-exercise baseline for the first time. Spirometry measurements were taken 5 mins prior to each exercise challenge & immediately, 5, 10, 15, 30, 45 & 60 mins after each exercise challenge. If participant had not returned to within 5% of the pre-exercise FEV1 value by 60 mins, then measurements were obtained at 75 & 90 mins. The 24-hour exercise challenges occurred 20-24 hours after the witnessed dose of medication. The analysis of efficacy data was carried out using a completers analysis population. This population included all randomized participants who received the witnessed dose of study drug in both active treatment periods, had at least one post-exercise FEV1 measurement in both active treatment periods, and had to have a baseline pre-exercise challenge FEV1.

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

End point timeframe:

0-60 minutes and 0-90 minutes after the exercise challenge at 24 hours postdose

| **End point values** | Montelukast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 62 | 62 | | |
| Units: Minutes | | | | |
| arithmetic mean (standard deviation) | 11.58 (± 16.51) | 18.46 (± 22.66) | | |

## Statistical analyses

| Statistical analysis title | Comparison between montelukast vs. placebo |
|---|---|
| Statistical analysis description: | |
| There were a total of 62 participants included in this analysis (cross-over design). | |
| Comparison groups | Montelukast v Placebo |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.054 |
| Method | ANOVA |
| Parameter estimate | Difference in least squares mean |
| Point estimate | -7.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.23 |
| upper limit | 0.11 |

## Secondary: Number of participants requiring rescue medication at 2 hours postdose

| End point title | Number of participants requiring rescue medication at 2 hours postdose |
|---|---|
| End point description: | |
| This endpoint was defined as the number of participants requiring rescue medication with β-agonist within the 90 mins following exercise challenge. The 2-hour exercise challenges occurred 2 hours after the witnessed dose of study medication. The analysis of efficacy data was carried out using a completers analysis population. This population included all randomized participants who received the witnessed dose of study drug in both active treatment periods and had at least one post-exercise FEV1 measurement in both active treatment periods. | |
| End point type | Secondary |
| End point timeframe: | |
| 0-90 minutes after the exercise challenge at 2 hours postdose | |

| End point values | Montelukast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 64 | 64 | | |
| Units: participants | | | | |
| number (not applicable) | 1 | 2 | | |

### Statistical analyses

| Statistical analysis title | Comparison between montelukast vs. placebo |
|---|---|
| Statistical analysis description: | |
| There were a total of 64 participants included in this analysis (cross-over design). | |
| Comparison groups | Montelukast v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 [1] |
| Method | Mcnemar |
| Parameter estimate | Difference in proportions |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.27 |
| upper limit | 5.63 |

Notes:

[1] - P-value provided is for comparison between the two proportions: Montelukast versus placebo.

## Secondary: Number of participants requiring rescue medication at 24 hours postdose

| | |
|---|---|
| End point title | Number of participants requiring rescue medication at 24 hours postdose |

End point description:

This endpoint was defined as the number of participants requiring rescue medication with β-agonist within the 90 mins following exercise challenge. The 24-hour exercise challenges occurred 20-24 hours after the witnessed dose of study medication. The analysis of efficacy data was carried out using a completers analysis population. This population included all randomized participants who received the witnessed dose of study drug in both active treatment periods and had at least one post-exercise FEV1 measurement in both active treatment periods.

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

End point timeframe:

0-90 minutes after the exercise challenge at 24 hours postdose

| **End point values** | Montelukast | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 62 | 62 | | |
| Units: Participants | | | | |
| number (not applicable) | 0 | 2 | | |

## Statistical analyses

| **Statistical analysis title** | Comparison between montelukast vs. placebo |
|---|---|

Statistical analysis description:

There were a total of 62 participants included in this analysis (cross-over design).

| | |
|---|---|
| Comparison groups | Montelukast v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in proportions |
| Point estimate | -3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.02 |
| upper limit | 3.06 |

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

Up to 24 days (including 14 days following the last dose of study drug)

Adverse event reporting additional description:

The analysis of safety data was carried out using an all participants as treated (APaT) population. This population included all randomized participants who received at least one dose of study treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 12.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Montelukast |

Reporting group description:

In Period 1 (screening period/ placebo run-in) participants received a single-blind dose of matching-image placebo. Participants 6-14 years of age were randomized to receive one montelukast 5-mg chewable tablet (single dose) in Period 2 or Period 3, according to the randomized treatment sequence assigned. Period 2 and Period 3 were separated by a washout period of 3-7 days.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

In Period 1 (screening period/ placebo run-in) participants received a single-blind dose of matching-image placebo. Participants 6-14 years of age were randomized to receive one matching placebo 5-mg chewable tablet (single dose) in Period 2 or Period 3, according to the randomized treatment sequence assigned. Period 2 and Period 3 were separated by a washout period of 3-7 days.

| **Serious adverse events** | Montelukast | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 66 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

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

| **Non-serious adverse events** | Montelukast | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 66 (0.00%) | |

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 non-serious adverse events occurred in greater than 5% of participants in any reporting group.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported