# Clinical trial results:
# A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Study Evaluating the Effects of 2 Different Regimens of Montelukast (Daily Dosing and Intermittent, Episode-Driven Dosing) Compared with Placebo in the Treatment of Episodic Asthma in Children Aged 6 Months to 5 Years

## Summary

| | |
|---|---|
| EudraCT number | 2006-002791-18 |
| Trial protocol | FI DK DE IT LT FR Outside EU/EEA |
| Global end of trial date | 12 August 2009 |

**Results information**

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

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 0476-302 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00337675 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | MK-0476-302: Merck Registration |

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) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000012-PIP01-07 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 12 August 2009 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 August 2009 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 August 2009 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the regimen-related efficacy of montelukast (daily dosing and intermittent, episode-driven dosing) compared with placebo in decreasing the number of asthma episodes culminating in asthma attack over a 52-week treatment period.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measure defined for this individual study was in place for the protection of trial subjects:
Participants were provided with short-acting ß-agonist (SABA; oral, inhaled or nebulized) which was to be used every 4 to 6 hours as needed throughout the study. The formulation of SABA was provided by investigators to participants according to the investigator's usual clinical practice.

Background therapy:

Participants were provided with SABA (oral, inhaled or nebulized) which was to be used every 4 to 6 hours as needed throughout the study. The formulation of SABA was provided by investigators to participants according to the investigator's usual clinical practice.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 29 September 2006 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 35 |
| Country: Number of subjects enrolled | Brazil: 77 |
| Country: Number of subjects enrolled | Canada: 27 |
| Country: Number of subjects enrolled | Chile: 228 |
| Country: Number of subjects enrolled | Colombia: 154 |
| Country: Number of subjects enrolled | Costa Rica: 251 |
| Country: Number of subjects enrolled | Guatemala: 120 |
| Country: Number of subjects enrolled | Israel: 47 |
| Country: Number of subjects enrolled | Mexico: 159 |
| Country: Number of subjects enrolled | Russian Federation: 139 |

| | |
|---|---|
| Country: Number of subjects enrolled | Singapore: 39 |
| Country: Number of subjects enrolled | South Africa: 98 |
| Country: Number of subjects enrolled | United States: 163 |
| Country: Number of subjects enrolled | Peru: 128 |
| Country: Number of subjects enrolled | Denmark: 13 |
| Country: Number of subjects enrolled | Finland: 30 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Germany: 31 |
| Country: Number of subjects enrolled | Italy: 24 |
| Country: Number of subjects enrolled | Lithuania: 3 |
| Worldwide total number of subjects | 1771 |
| EEA total number of subjects | 106 |

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) | 277 |
| Children (2-11 years) | 1494 |
| Adolescents (12-17 years) | 0 |
| 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:

Pediatric participants who were 6 months to 5 years of age and had episodic asthma were screened for this study.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Daily Montelukast |

Arm description:

Participants received montelukast 4-5 mg (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of matching placebo (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Montelukast |
| Investigational medicinal product code | |
| Other name | MK-0476 |
| Pharmaceutical forms | Chewable tablet, Granules |
| Routes of administration | Oral use |

Dosage and administration details:

Montelukast 4-5 mg, once daily at bedtime for 52 weeks

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

Dosage and administration details:

Placebo, once daily at bedtime for 12 days as needed for symptoms of imminent respiratory infection or episode of breathing problems

| | |
|---|---|
| **Arm title** | Intermittent Montelukast |

Arm description:

Participants received placebo (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of montelukast 4-5 mg (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

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

| | |
|---|---|
| Dosage and administration details: | |
| Placebo, once daily at bedtime for 52 weeks | |
| Investigational medicinal product name | Montelukast |
| Investigational medicinal product code | |
| Other name | MK-0476 |
| Pharmaceutical forms | Chewable tablet, Granules |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Montelukast 4-5 mg, once daily at bedtime for 12 days as needed for symptoms of imminent respiratory infection or episode of breathing problems | |
| **Arm title** | Placebo |
| Arm description: | |
| Participants received placebo (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of placebo (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Chewable tablet, Granules |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Placebo, once daily at bedtime for 52 weeks | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Chewable tablet, Granules |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Placebo, once daily at bedtime for 12 days as needed for symptoms of imminent respiratory infection or episode of breathing problems | |

| **Number of subjects in period 1** | Daily Montelukast | Intermittent Montelukast | Placebo |
|---|---|---|---|
| Started | 589 | 591 | 591 |
| Treated | 587 | 589 | 590 |
| Completed | 492 | 488 | 492 |
| Not completed | 97 | 103 | 99 |
| Physician decision | 9 | 17 | 14 |
| Consent withdrawn by subject | 25 | 25 | 19 |
| Trial terminated | - | - | 2 |
| Adverse event, non-fatal | 10 | 9 | 19 |
| Lost to follow-up | 22 | 19 | 17 |
| Progressive disease | - | 2 | - |
| Lack of efficacy | 10 | 7 | 9 |
| Protocol deviation | 21 | 24 | 19 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Daily Montelukast |

Reporting group description:

Participants received montelukast 4-5 mg (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of matching placebo (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

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

Reporting group description:

Participants received placebo (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of montelukast 4-5 mg (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

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

Reporting group description:

Participants received placebo (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of placebo (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

| Reporting group values | Daily Montelukast | Intermittent Montelukast | Placebo |
|---|---|---|---|
| Number of subjects | 589 | 591 | 591 |
| Age categorical | | | |
| Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 86 | 92 | 99 |
| Children (2-11 years) | 503 | 499 | 492 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 239 | 226 | 238 |
| Male | 350 | 365 | 353 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 1771 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 277 | | |
| Children (2-11 years) | 1494 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 703 | | |
| Male | 1068 | | |

## End points

### End points reporting groups

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

Reporting group description:

Participants received montelukast 4-5 mg (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of matching placebo (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

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

Reporting group description:

Participants received placebo (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of montelukast 4-5 mg (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

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

Reporting group description:

Participants received placebo (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of placebo (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

### Primary: Number of Asthma Episodes Culminating in Asthma Attack Over the 52-week Treatment Period

| End point title | Number of Asthma Episodes Culminating in Asthma Attack Over the 52-week Treatment Period |
|---|---|

End point description:

The rate per year of asthma episodes culminating in an asthma attack is presented. An asthma episode started the day intermittent treatment was initiated. An asthma episode ended when intermittent treatment of the episode was stopped (treatment lasted for 12 calendar days) or when a "No" was recorded for both questions on the Symptom Calendar, whichever was longer. Asthma attacks were defined as respiratory symptoms requiring healthcare resource utilization (HRU), which comprised unscheduled visits to a physician or emergency department, treatment with corticosteroids (oral, rectal or inhaled), or hospitaliation. Each day during an asthma episode, the participant's guardian recorded all the HRU that was required spcifically for breathing problems.

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

End point timeframe:

52 weeks

| End point values | Daily Montelukast | Intermittent Montelukast | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 584[1] | 588[2] | 585[3] | |
| Units: Number of asthma episodes | | | | |
| arithmetic mean (confidence interval 95%) | 0.99 (0.86 to 1.14) | 1.06 (0.92 to 1.22) | 1.05 (0.92 to 1.2) | |

Notes:

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

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

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

## Statistical analyses

| **Statistical analysis title** | Rate Ratio of Daily Montelukast vs. Placebo |
|---|---|

Statistical analysis description:

Rate ratio of Daily Montelukast compared to Placebo for the number of asthma episodes culminating in asthma attacks. Analysis is based on Poisson regression with factors for treatment, age category and geographical region.

| | |
|---|---|
| Comparison groups | Daily Montelukast v Placebo |
| Number of subjects included in analysis | 1169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.51 [4] |
| Method | Poisson Regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.11 |

Notes:

[4] - Multiplicity adjustment across regimens was addressed through step-down testing. Daily Montelukast vs. Placebo was tested first; if this comparison was significant, Intermittent Montelukast vs. Placebo was tested. The significance level was 5%.

| **Statistical analysis title** | Rate Ratio of Intermittent Montelukast vs. Placebo |
|---|---|

Statistical analysis description:

Rate ratio of Intermittent Montelukast compared to Placebo for the number of asthma episodes culminating in asthma attacks. Analysis is based on Poisson regression with factors for treatment, age category and geographical region.

| | |
|---|---|
| Comparison groups | Intermittent Montelukast v Placebo |
| Number of subjects included in analysis | 1173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.884 [5] |
| Method | Poisson Regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.19 |

Notes:

[5] - Multiplicity adjustment across regimens was addressed through step-down testing. Daily Montelukast vs. Placebo was tested first; if this comparison was significant, Intermittent Montelukast vs. Placebo was tested. The significance level was 5%.

## Secondary: Daily Average of Wheeze and Difficulty Breathing Score in the 3 Days Prior to Start of Asthma Attack

| End point title | Daily Average of Wheeze and Difficulty Breathing Score in the 3 Days Prior to Start of Asthma Attack |
|---|---|

End point description:

Each day during an asthma episode, the participant's guardian was asked to rate each of the symptoms of wheeze and difficulty breathing on a 6-point scale (0=best to 5=worst). The average of the individual symptom scores on each of the 3 days prior to an asthma attack was calculated. If a participant had multiple episodes during the 52-week study period, the symptom scores were averaged across all episodes. Only participants who experienced an asthma attack within an episode and did not start their intermittent study drug on the day of the attack were included in this analysis.

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

End point timeframe:

52 weeks

| End point values | Daily Montelukast | Intermittent Montelukast | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 138[6] | 162[7] | 152[8] | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | 1.69 (1.49 to 1.88) | 1.7 (1.52 to 1.89) | 1.88 (1.69 to 2.07) | |

Notes:

[6] - Participants who had an asthma attack and did not start intermittent study drug on day of attack.

[7] - Participants who had an asthma attack and did not start intermittent study drug on day of attack.

[8] - Participants who had an asthma attack and did not start intermittent study drug on day of attack.

### Statistical analyses

| Statistical analysis title | Difference in Pre-attack Scores |
|---|---|

Statistical analysis description:

Difference in least squares (LS) means of Daily Montelukast compared to Placebo for the daily average of wheeze and difficulty breathing score in the 3 days prior to the start of an asthma attack. Analysis based on analysis of variance (ANOVA) with terms for treatment, age category and geographical region.

| Comparison groups | Daily Montelukast v Placebo |
|---|---|
| Number of subjects included in analysis | 290 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.176 [9] |
| Method | ANOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.09 |

Notes:

[9] - Multiplicity adjustment across regimens and across primary and secondary end points was addressed through step-down testing. Within the 2 secondary end points assessing severity, adjustment for multiplicity was performed using Hochberg's method.

| Statistical analysis title | Difference in Pre-attack Scores |
|---|---|

Statistical analysis description:

Difference in LS means of Intermittent Montelukast compared to Placebo for the daily average of wheeze and difficulty breathing score in the 3 days prior to the start of an asthma attack. Analysis based on ANOVA with terms for treatment, age category and geographical region.

| | |
|---|---|
| Comparison groups | Intermittent Montelukast v Placebo |
| Number of subjects included in analysis | 314 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.202 [10] |
| Method | ANOVA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | 0.09 |

Notes:

[10] - Multiplicity adjustment across regimens and across primary and secondary end points was addressed through step-down testing. Within the 2 secondary end points assessing severity, adjustment for multiplicity was performed using Hochberg's method.

## Secondary: Daily Average of Wheeze, Difficulty Breathing, Daytime Cough, and Interference with Daily Activity Score Over the 12-day Treatment Period of an Asthma Episode (Before Asthma Attack)

| | |
|---|---|
| End point title | Daily Average of Wheeze, Difficulty Breathing, Daytime Cough, and Interference with Daily Activity Score Over the 12-day Treatment Period of an Asthma Episode (Before Asthma Attack) |

End point description:

Each day during an asthma episode, the participant's guardian was asked to rate each of the symptoms of wheeze, difficulty breathing, daytime cough, and interference with daily activity on a 6-point scale (0=best to 5=worst). The average of the individual symptoms on each of the 12 days of intermittent treatment for an asthma episode (before the first attack) was reported. If a participant had multiple episodes over the 52-week treatment period, the symptom scores were averaged across all the episodes. Only participants who had ≥1 asthma episode that culminated in an asthma attack were included in the analysis.

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

End point timeframe:

52 weeks

| End point values | Daily Montelukast | Intermittent Montelukast | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 365[11] | 387[12] | 368[13] | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | 1.08 (1 to 1.16) | 1.09 (1.01 to 1.17) | 1.2 (1.12 to 1.28) | |

Notes:

[11] - Participants who had ≥1 asthma episode that culminated in an asthma attack.

[12] - Participants who had ≥1 asthma episode that culminated in an asthma attack.

[13] - Participants who had ≥1 asthma episode that culminated in an asthma attack.

## Statistical analyses

| **Statistical analysis title** | Difference in Asthma Episode Scores |
|---|---|

Statistical analysis description:

Difference in LS means of Daily Montelukast compared to Placebo for daily average of wheeze, difficulty breathing, daytime cough, and interference with daily activity score over the 12-day treatment period of an asthma episode (before attack). Analysis based on ANOVA with terms for treatment, age category and geographical region.

| Comparison groups | Daily Montelukast v Placebo |
|---|---|
| Number of subjects included in analysis | 733 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.045 [14] |
| Method | ANOVA |
| Parameter estimate | Difference in LS means |
| Point estimate | -0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | 0 |

Notes:

[14] - Multiplicity adjustment across regimens and across primary and secondary end points was addressed through step-down testing. Within the 2 secondary end points assessing severity, adjustment for multiplicity was performed using Hochberg's method.

| **Statistical analysis title** | Difference in Asthma Episode Scores |
|---|---|

Statistical analysis description:

Difference in LS means of Intermittent Montelukast compared to Placebo for daily average of wheeze, difficulty breathing, daytime cough, and interference with daily activity score over the 12-day treatment period of an asthma episode (before attack). Analysis based on ANOVA with terms for treatment, age category and geographical region.

| Comparison groups | Intermittent Montelukast v Placebo |
|---|---|
| Number of subjects included in analysis | 755 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.061 [15] |
| Method | ANOVA |
| Parameter estimate | Difference in LS means |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | 0 |

Notes:

[15] - Multiplicity adjustment across regimens and across primary and secondary end points was addressed through step-down testing. Within the 2 secondary end points assessing severity, adjustment for multiplicity was performed using Hochberg's method.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

52 weeks

Adverse event reporting additional description:

Population includes all randomized participants who received ≥1 dose of study drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 12.0 |

### Reporting groups

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

Reporting group description:

Participants received montelukast 4-5 mg (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of matching placebo (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

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

Reporting group description:

Participants received placebo (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of montelukast 4-5 mg (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

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

Reporting group description:

Participants received placebo (chewable tablets or oral granules, depending on participant age) once daily at bedtime for 52 weeks plus intermittent 12-day courses of matching placebo (chewable tablets or oral granules) once daily at bedtime (a course was initiated as needed for symptoms of imminent respiratory infection or episode of breathing problems) during the 52-week study period.

| **Serious adverse events** | Daily Montelukast | Intermittent Montelukast | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 28 / 584 (4.79%) | 41 / 588 (6.97%) | 33 / 585 (5.64%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Accidental poisoning | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Hydrocele | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile convulsion | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 1 / 588 (0.17%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Lymphadenitis | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 584 (0.17%) | 1 / 588 (0.17%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 13 / 584 (2.23%) | 17 / 588 (2.89%) | 14 / 585 (2.39%) |
| occurrences causally related to treatment / all | 0 / 17 | 0 / 20 | 1 / 16 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthmatic crisis | | | |
| subjects affected / exposed | 2 / 584 (0.34%) | 4 / 588 (0.68%) | 3 / 585 (0.51%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stridor | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Synovitis | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenoiditis | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenovirus infection | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 2 / 588 (0.34%) | 2 / 585 (0.34%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Croup infectious | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis viral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis A | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis viral | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Kawasaki's disease | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngotracheitis obstructive | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lobar pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parotid abscess | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 584 (0.51%) | 4 / 588 (0.68%) | 4 / 585 (0.68%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia mycoplasmal | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia primary atypical | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 584 (0.34%) | 2 / 588 (0.34%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicella | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 1 / 588 (0.17%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral diarrhoea | | | |
| subjects affected / exposed | 0 / 584 (0.00%) | 0 / 588 (0.00%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral rash | | | |
| subjects affected / exposed | 1 / 584 (0.17%) | 0 / 588 (0.00%) | 0 / 585 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 584 (0.17%) | 1 / 588 (0.17%) | 1 / 585 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Daily Montelukast | Intermittent Montelukast | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 481 / 584 (82.36%) | 506 / 588 (86.05%) | 486 / 585 (83.08%) |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 94 / 584 (16.10%) | 87 / 588 (14.80%) | 80 / 585 (13.68%) |
| occurrences (all) | 148 | 133 | 139 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 35 / 584 (5.99%) | 49 / 588 (8.33%) | 43 / 585 (7.35%) |
| occurrences (all) | 49 | 61 | 45 |
| Vomiting | | | |
| subjects affected / exposed | 22 / 584 (3.77%) | 31 / 588 (5.27%) | 30 / 585 (5.13%) |
| occurrences (all) | 26 | 38 | 38 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 332 / 584 (56.85%) | 338 / 588 (57.48%) | 319 / 585 (54.53%) |
| occurrences (all) | 834 | 944 | 807 |
| Cough | | | |
| subjects affected / exposed | 91 / 584 (15.58%) | 101 / 588 (17.18%) | 93 / 585 (15.90%) |
| occurrences (all) | 261 | 259 | 266 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 46 / 584 (7.88%) | 44 / 588 (7.48%) | 31 / 585 (5.30%) |
| occurrences (all) | 64 | 62 | 40 |
| Wheezing | | | |
| subjects affected / exposed | 33 / 584 (5.65%) | 31 / 588 (5.27%) | 37 / 585 (6.32%) |
| occurrences (all) | 87 | 87 | 103 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Bronchitis | | | |
| subjects affected / exposed | 33 / 584 (5.65%) | 40 / 588 (6.80%) | 32 / 585 (5.47%) |
| occurrences (all) | 60 | 72 | 72 |
| Influenza | | | |
| subjects affected / exposed | 30 / 584 (5.14%) | 31 / 588 (5.27%) | 27 / 585 (4.62%) |
| occurrences (all) | 59 | 54 | 51 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 110 / 584 (18.84%) | 110 / 588 (18.71%) | 81 / 585 (13.85%) |
| occurrences (all) | 253 | 230 | 198 |
| Otitis media | | | |
| subjects affected / exposed | 44 / 584 (7.53%) | 55 / 588 (9.35%) | 45 / 585 (7.69%) |
| occurrences (all) | 63 | 70 | 62 |
| Pharyngitis | | | |
| subjects affected / exposed | 59 / 584 (10.10%) | 64 / 588 (10.88%) | 67 / 585 (11.45%) |
| occurrences (all) | 75 | 82 | 84 |
| Rhinitis | | | |
| subjects affected / exposed | 36 / 584 (6.16%) | 33 / 588 (5.61%) | 30 / 585 (5.13%) |
| occurrences (all) | 61 | 52 | 42 |
| Sinusitis | | | |
| subjects affected / exposed | 39 / 584 (6.68%) | 49 / 588 (8.33%) | 27 / 585 (4.62%) |
| occurrences (all) | 51 | 62 | 38 |
| Tonsillitis | | | |
| subjects affected / exposed | 38 / 584 (6.51%) | 42 / 588 (7.14%) | 37 / 585 (6.32%) |
| occurrences (all) | 41 | 44 | 41 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 81 / 584 (13.87%) | 76 / 588 (12.93%) | 82 / 585 (14.02%) |
| occurrences (all) | 189 | 172 | 184 |
| Varicella | | | |
| subjects affected / exposed | 36 / 584 (6.16%) | 15 / 588 (2.55%) | 28 / 585 (4.79%) |
| occurrences (all) | 36 | 15 | 28 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 28 June 2006 | Amendment 01: The Pre-Episode Symptom List was added to be reviewed with the study coordinator to identify symptoms the participant usually experiences prior to developing an episode of breathing problems. General: "Respiratory Symptom Calendar" was changed to "Symptom Calendar". References to respiratory symptoms were removed and aligned with symptoms chosen by the parent/guardian on the Pre-Episode Symptom List. "Supplemental Medication" was changed to "Episode Medication". In Episode Diary, the question on severity of nose symptoms was removed. Used medication and health resource utilization (HRU) for "breathing problems" instead of "respiratory symptoms". Question on HRU was added: "What made you take your child for this visit?" with a space for the response. |
| 22 March 2007 | Amendment 02: The main reasons for this amendment were to include a younger population of participants, specifically pediatric participants aged 12 to 23 months, and to address clarifications requested by investigators and study coordinators. The sample size was increased 1700 participants from 1350 participants. All references and descriptions of study medication were changed to reflect the addition of the oral granule formulation of montelukast and matching placebo that would be used in participants aged 12 to 23 months. |
| 13 December 2007 | Amendment 03: The main reason for this amendment was to include a younger population of participants, specifically those aged 6 to 12 months. Also the updated United States (US) Product Circular and US Patient Product Information were added. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported