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