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 Units: Subjects			
Age Continuous Units: years			
arithmetic mean	10.9	11.5	
standard deviation	± 2.3	± 1.8	-
Gender, Male/Female 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