Clinical trial results:
A Multicenter, Double-Blind, Randomized, Cross-Over Design Study to Evaluate the Effect of Montelukast vs. Salmeterol on the Inhibition of Exercise-Induced Bronchoconstriction in Asthmatic Patients Aged 6-14 Years.

Summary

EudraCT number	2004-004709-53
Trial protocol	EE ES IT Outside EU/EEA
Global end of trial date	14 November 2008

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	MK-0476-911

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00127166
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-0476-911

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	14 November 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2008
Global end of trial reached?	Yes
Global end of trial date	14 November 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the effect of four weeks of treatment with two investigational drugs (oral versus inhaled administration) plus an inhaled medication in the treatment of airway constriction brought on by exercise in participants with asthma.

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: salbutamol was to be used
throughout all periods on an “as needed” basis for rescue.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2005
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	Spain: 2
Country: Number of subjects enrolled	Estonia: 17
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Brazil: 41
Country: Number of subjects enrolled	Colombia: 25
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Peru: 20
Country: Number of subjects enrolled	Poland: 14
Worldwide total number of subjects	154
EEA total number of subjects	60

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)	112
Adolescents (12-17 years)	42
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:

For randomization, participants fulfilled the following criteria: 1. Forced Expiratory Volume in one second (FEV1) ≥70% predicted while withholding beta (β)-agonist for at least 6 hours 2. Exercise-induced bronchoconstriction (EIB) showing FEV1 ≥15% reduction from baseline while on inhaled corticosteroids demonstrated twice during the run-in period

Period 1

Period 1 title	Period I
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Montelukast / Salmeterol

Arm description:

Period I- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo dry powder inhaler (DPI) twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.

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

Dosage and administration details:

Montelukast 5 mg oral tablet once daily

Investigational medicinal product name	Salmeterol matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Matching placebo to salmeterol dry powder for inhalation administered twice daily

Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Flixotide Evohaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

Arm title	Salmeterol / Montelukast

Arm description:

Period I- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching

placebo). Period II- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.

Arm type	Experimental
Investigational medicinal product name	Salmeterol xinafoate
Investigational medicinal product code	
Other name	Serevent Accuhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol 50 mcg dry powder per actuation inhaled twice daily

Investigational medicinal product name	Montelukast matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to montelukast oral tablet administered once daily

Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Flixotide Evohaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

Number of subjects in period 1	Montelukast / Salmeterol	Salmeterol / Montelukast
Started	78	76
Completed	75	74
Not completed	3	2
Consent withdrawn by subject	2	-
Participant did not meet inclusion criteria	1	-
Protocol deviation	-	2

Period 2

Period 2 title	Washout Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes

Arm title	Montelukast / Salmeterol

Arm description:

Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Flixotide Evohaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

Investigational medicinal product name	Salmeterol matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Matching placebo to salmeterol dry powder for inhalation administered twice daily

Investigational medicinal product name	Montelukast matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to montelukast oral tablet administered once daily

Arm title	Salmeterol / Montelukast

Arm description:

Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Flixotide Evohaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

Investigational medicinal product name	Salmeterol matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Matching placebo to salmeterol dry powder for inhalation administered twice daily

Investigational medicinal product name	Montelukast matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet

Routes of administration	Oral use

Dosage and administration details:

Matching placebo to montelukast oral tablet administered once daily

Number of subjects in period 2	Montelukast / Salmeterol	Salmeterol / Montelukast
Started	75	74
Completed	75	73
Not completed	0	1
Participant did not meet inclusion criteria	-	1

Period 3

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Montelukast / Salmeterol

Arm description:

Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Arm type	Experimental
Investigational medicinal product name	Montelukast matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to montelukast oral tablet administered once daily

Investigational medicinal product name	Salmeterol xinafoate
Investigational medicinal product code	
Other name	Serevent Accuhaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol 50 mcg dry powder per actuation inhaled twice daily

Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Flixotide Evohaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

Arm title	Salmeterol / Montelukast

Arm description:

Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

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

Dosage and administration details:

Montelukast 5 mg oral tablet once daily

Investigational medicinal product name	Salmeterol matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Matching placebo to salmeterol dry powder inhaler administered twice daily

Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	Flixotide Evohaler
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

Number of subjects in period 3	Montelukast / Salmeterol	Salmeterol / Montelukast
Started	75	73
Completed	72	73
Not completed	3	0
Consent withdrawn by subject	2	-
Participant did not perform last visit exercise	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Montelukast / Salmeterol
Reporting group description:	
Period I- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo dry powder inhaler (DPI) twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.	
Reporting group title	Salmeterol / Montelukast
Reporting group description:	
Period I- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.	

Reporting group values	Montelukast / Salmeterol	Salmeterol / Montelukast	Total
Number of subjects	78	76	154
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	10.2	9.8	
standard deviation	± 2	± 2	-
Gender categorical			
Units: Subjects			
Female	35	30	65
Male	43	46	89
Race			
Units: Subjects			
Asian	1	0	1
Black	11	7	18
White	38	41	79
Hispanic	15	18	33
Multiracial	13	10	23
Area under the curve from 0 to 20 minutes (AUC(0-20))			
Area Under the Curve for percent-change from pre-exercise baseline FEV1 in liters, from 0 to 20 minutes (AUC(0-20))			
Units: Percent times minutes			
arithmetic mean	320.08	317.74	
standard deviation	± 208.62	± 165.71	-
Avg %-change from pre-exercise baseline FEV1 after 1st β-agonist use & Prior to 2nd β-agonist use			
Average (avg) percent (%)-change from pre-exercise baseline FEV1 after 1st β-agonist use & prior to 2nd β-agonist use			
Units: Percent change from baseline			
arithmetic mean	1.36	4.78	
standard deviation	± 10.99	± 10.92	-

Maximum FEV1 Percent Predicted			
Units: Percent of predicted value			
arithmetic mean	99.88	100.54	
standard deviation	± 32.45	± 15.61	-
Maximum Percent Fall in FEV1 After Exercise			
Units: Percent change from baseline			
arithmetic mean	24.77	25.42	
standard deviation	± 10.25	± 9.04	-
Time to recovery			
Population includes participants who returned to within 5% of the baseline FEV1 value. Montelukast / Salmeterol, n=71; Salmeterol / Montelukast, n=70			
Units: Minutes			
arithmetic mean	23.53	21.51	
standard deviation	± 10.53	± 8.3	-

End points

End points reporting groups

Reporting group title	Montelukast / Salmeterol

Reporting group description:

Period I- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo dry powder inhaler (DPI) twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.

Reporting group title	Salmeterol / Montelukast

Reporting group description:

Period I- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.

Reporting group title	Montelukast / Salmeterol

Reporting group description:

Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Reporting group title	Salmeterol / Montelukast

Reporting group description:

Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Reporting group title	Montelukast / Salmeterol

Reporting group description:

Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Reporting group title	Salmeterol / Montelukast

Reporting group description:

Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Subject analysis set title	Montelukast
Subject analysis set type	Full analysis

Subject analysis set description:

The primary efficacy analysis was based on the full analysis set (FAS) population which included all randomized participants who took at least one dose of post randomization study drug and had a measurement for analysis available in both treatment periods of the cross-over design.

Subject analysis set title	Salmeterol
Subject analysis set type	Full analysis

Subject analysis set description:

The primary efficacy analysis was based on the full analysis set (FAS) population which included all randomized participants who took at least one dose of post randomization study drug and had a measurement for analysis available in both treatment periods of the cross-over design.

Primary: Maximum post-exercise percent fall in FEV1

End point title	Maximum post-exercise percent fall in FEV1

End point description:

The effect of four weeks of treatment with oral montelukast plus inhaled fluticasone, and inhaled salmeterol plus inhaled fluticasone on EIB as measured by the maximum post-exercise percent fall (relative to pre-exercise baseline) in FEV1.

End point type	Primary

End point timeframe:

4 weeks (Weeks 0 to 4 or Weeks 6 to 10)

End point values	Montelukast	Salmeterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: Percent change from baseline				
least squares mean (confidence interval 95%)	10.57 (8.86 to 12.27)	13.82 (12.11 to 15.52)		

Statistical analyses

Statistical analysis title	Difference in least squares mean

Statistical analysis description:

There were a total of 144 participants included in this analysis (cross-over design).

Comparison groups	Montelukast v Salmeterol
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 [1]
Method	ANOVA
Parameter estimate	Least squares mean difference
Point estimate	-3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.66
upper limit	-0.84

Notes:

[1] - Model terms: participant, treatment and period. The treatment test is adjusted for period.

Secondary: Area under the curve for percent-change from pre-exercise baseline FEV1 in liters, from 0 to 20 Minutes (AUC(0-20))

End point title	Area under the curve for percent-change from pre-exercise baseline FEV1 in liters, from 0 to 20 Minutes (AUC(0-20))

End point description:

The effect of a four-week treatment course of oral montelukast plus inhaled fluticasone, compared to inhaled salmeterol plus inhaled fluticasone, on the extent and severity of EIB as measured by the area under the curve from 0 to 20 minutes (AUC0-20) for FEV1 percent change from pre-exercise baseline.

End point type	Secondary

End point timeframe:

4 weeks (Weeks 0 to 4 or Weeks 6 to 10)

End point values	Montelukast	Salmeterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: Percent times minutes				
least squares mean (confidence interval 95%)	116.04 (89.95 to 142.24)	168.75 (142.56 to 194.95)		

Statistical analyses

Statistical analysis title	Difference in least squares mean

Statistical analysis description:

There were a total of 144 participants included in this analysis (cross-over design).

Comparison groups	Montelukast v Salmeterol
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006 [2]
Method	ANOVA
Parameter estimate	Least squares mean difference
Point estimate	-52.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-89.76
upper limit	-15.66

Notes:

[2] - Model terms: participant, treatment and period. The treatment test is adjusted for period.

Secondary: Maximum FEV1 percent predicted following first β-agonist use

End point title	Maximum FEV1 percent predicted following first β-agonist use

End point description:

The effect of a four-week treatment course of oral montelukast plus inhaled fluticasone, compared to inhaled salmeterol plus inhaled fluticasone, on short-acting β-agonist bronchodilation as measured by the maximum FEV1 percent predicted following first β-agonist use.

End point type	Secondary

End point timeframe:

4 weeks (Weeks 0 to 4 or Weeks 6 to 10)

End point values	Montelukast	Salmeterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: Percent of predicted value				
least squares mean (confidence interval 95%)	104.03 (102.83 to 105.23)	99.92 (98.72 to 101.12)		

Statistical analyses

Statistical analysis title	Difference in least squares mean

Statistical analysis description:

There were a total of 144 participants included in this analysis (cross-over design).

Comparison groups	Montelukast v Salmeterol
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [3]
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	4.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.58
upper limit	5.64

Notes:

[3] - Terms: participant, treatment, period & covariate for FEV1 %-predicted at pre-exercise baseline.

Secondary: Time to recovery to within 5 percent of baseline FEV1

End point title	Time to recovery to within 5 percent of baseline FEV1

End point description:

The effect of a four-week treatment course of oral montelukast plus inhaled fluticasone, compared to inhaled salmeterol plus inhaled fluticasone, on the extent and severity of EIB as measured by the time to recovery (to within 5 percent of the pre-exercise baseline FEV1) following a standardized exercise challenge.

End point type	Secondary

End point timeframe:

4 weeks (Weeks 0 to 4 or Weeks 6 to 10)

End point values	Montelukast	Salmeterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: minutes				
median (inter-quartile range (Q1-Q3))	5.9 (0 to 19.12)	11.1 (0.065 to 22.94)		

Statistical analyses

Statistical analysis title	Comparison between montelukast vs. salmeterol

Statistical analysis description:

There were a total of 144 participants included in this analysis (cross-over design).

Comparison groups	Montelukast v Salmeterol
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.035 [5]
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.55

Notes:

[4] - A robust estimate of the variance of the treatment effect was calculated using the marginal approach introduced by Wei, Lin and Weissfeld (WLW model).
[5] - Model terms: treatment and period.

Secondary: Average percent-change in FEV1 after first β-agonist use and prior to second β-agonist use

End point title	Average percent-change in FEV1 after first β-agonist use and prior to second β-agonist use

End point description:

The effect of a four-week treatment course of oral montelukast plus inhaled fluticasone, compared to inhaled salmeterol plus inhaled fluticasone, on the extent and severity of EIB as measured by the average percent change in FEV1 after first β-agonist intake and prior to second β-agonist use.

End point type	Secondary

End point timeframe:

4 weeks (Weeks 0 to 4 or Weeks 6 to 10)

End point values	Montelukast	Salmeterol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: Percent change from baseline				
least squares mean (confidence interval 95%)	6.51 (5.44 to 7.59)	2.72 (1.64 to 3.79)		

Statistical analyses

Statistical analysis title	Difference in least squares mean
Statistical analysis description:	
There were a total of 144 participants included in this analysis (cross-over design).	
Comparison groups	Montelukast v Salmeterol
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [6]
Method	ANOVA
Parameter estimate	Least squares mean difference
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.28
upper limit	5.32

Notes:

[6] - Model terms: participant, treatment and period. The treatment test is adjusted for period.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 12 weeks (including 2 weeks following last dose of study drug)

Adverse event reporting additional description:

Of 154 participants enrolled, only 150 took at least 1 dose of each treatment (tx); 78 were in Montelukast (M) /Salmeterol (S) sequence (seq) and 76 in S/M seq. 4 participants in M/S seq only took 1st tx; so 78 took M & 74 took S. 4 different participants in S/M seq only took 1st tx; so 76 took S & 72 took M. Total 150 pts took M and 150 took S.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Montelukast

Reporting group description:

Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Reporting group title	Salmeterol

Reporting group description:

Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Period II- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

Serious adverse events	Montelukast	Salmeterol	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 150 (0.67%)	1 / 150 (0.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Montelukast	Salmeterol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 150 (18.00%)	21 / 150 (14.00%)	
Injury, poisoning and procedural complications			
Ear injury			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 150 (0.67%)	1 / 150 (0.67%)	
occurrences (all)	1	1	
Skin injury			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 150 (1.33%)	0 / 150 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 150 (0.00%)	2 / 150 (1.33%)	
occurrences (all)	0	2	
Immune system disorders			
Allergy to plants			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			

subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis allergic			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 150 (1.33%)	0 / 150 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 150 (2.67%)	4 / 150 (2.67%)	
occurrences (all)	4	4	
Bronchospasm			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	1 / 150 (0.67%)	1 / 150 (0.67%)	
occurrences (all)	1	1	

Skin lesion			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences (all)	0	1	
Infections and infestations			
Candidiasis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 150 (0.67%)	1 / 150 (0.67%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	2 / 150 (1.33%)	1 / 150 (0.67%)	
occurrences (all)	2	1	
Pertussis			
subjects affected / exposed	2 / 150 (1.33%)	0 / 150 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	5 / 150 (3.33%)	3 / 150 (2.00%)	
occurrences (all)	5	3	
Pneumonia			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	3 / 150 (2.00%)	2 / 150 (1.33%)	
occurrences (all)	3	2	
Upper respiratory tract infection			

subjects affected / exposed	1 / 150 (0.67%)	1 / 150 (0.67%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	0 / 150 (0.00%)	2 / 150 (1.33%)	
occurrences (all)	0	2	
Viral pharyngitis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	
Viral rhinitis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2005	Amendment 1: Primary reason for the amendment was to update the salmeterol dosage to salmeterol/matching placebo drug powder inhaler (DPI) formulation 50 mcg/puff, one puff twice daily, total dose of 100 mcg/day. Use of spacer device with salmeterol was deleted.
16 January 2007	Amendment 2: Primary reason for the amendment was that participants must demonstrate exercise induced bronchoconstriction with post-exercise decline in FEV1 of 15 % (change from 20 %).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported