Clinical trial results:
Korean Study of "Real-World" Montelukast Use in Mild Asthmatic Children With Concomitant Allergic Rhinitis

Summary

EudraCT number	2014-004748-37
Trial protocol	Outside EU/EEA
Global end of trial date	24 October 2007

Results information

Result version number	v3 (current)
This version publication date	21 August 2016
First version publication date	19 July 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	0476-367

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00442559
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	24 October 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess real-world effectiveness of montelukast in children (2 to 14 years) with asthma and allergic rhinitis.

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 measures defined for this individual study were in place for the protection of subjects: adjunct daily inhaler (nebulized salbutamol) therapy on an as needed basis; rescue oral, intramuscular, or intravenous corticosteroid therapy for asthma attacks; and addition of inhaled corticosteroids to study treatments for exacerbation from mild to moderate asthma.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	18 January 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 191
Worldwide total number of subjects	191
EEA total number of subjects	0

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)	177
Adolescents (12-17 years)	14
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Conducted at 5 sites in Korea, Feb2005~ Dec2007 in pediatric participants with comorbid mild asthma and allergic rhinitis. Participant's caregiver understands the study procedures and agrees to participate, signing the informed consent form. Additional inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

Up to 1 week for wash-out - prior to baseline randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Montelukast

Arm description:

Participants were treated for 12 months after randomization: Participants 2 to 5 years of age took one 4 mg chewable tablet and 6 to 14 years of age took one 5 mg chewable tablet daily in the evening. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

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

Dosage and administration details:

Montelukast 4/5 mg tablet (oral chewable), once daily, 12 weeks to up to 12 months

Arm title	Inhaled Corticosteroids (ICS)

Arm description:

Participants were treated for 12 months after randomization: Each participant's physician selected the ICS agent, dose, and regimen. If participants had exacerbated from mild to moderate within 12 weeks, ICS was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	inhaled corticosteroid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Inhaled corticosteroid solution, 1-4 puffs daily, 12 weeks to up to 12 months

Number of subjects in period 1	Montelukast	Inhaled Corticosteroids (ICS)
Started	100	91
12 weeks after randomization	68	60
Completed	66	56
Not completed	34	35
Consent withdrawn by subject	1	-
Lost to follow-up	32	34
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Montelukast
Reporting group description:	
Participants were treated for 12 months after randomization: Participants 2 to 5 years of age took one 4 mg chewable tablet and 6 to 14 years of age took one 5 mg chewable tablet daily in the evening. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.	
Reporting group title	Inhaled Corticosteroids (ICS)
Reporting group description:	
Participants were treated for 12 months after randomization: Each participant's physician selected the ICS agent, dose, and regimen. If participants had exacerbated from mild to moderate within 12 weeks, ICS was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.	

Reporting group values	Montelukast	Inhaled Corticosteroids (ICS)	Total
Number of subjects	100	91	191
Age categorical Units: Subjects			
Age Continuous			
24 participants were included in the Montelukast group and 29 participants were included in the ICS group.			
Units: years			
arithmetic mean	5.4	6.1	
standard deviation	± 3	± 2.6	-
Gender, Male/Female Units: participants			
Female	5	9	14
Male	19	20	39
Not reported	76	62	138
Allergic rhinitis			
Based on GINA guidelines.			
Units: Subjects			
Mild-intermittent	14	17	31
Mild-persistent	10	12	22
Not reported	76	62	138
Type of allergic rhinitis Units: Subjects			
Seasonal	13	15	28
Perennial	11	14	25
Not reported	76	62	138
Daily allergic rhinitis symptom score			
The score is an ordinal scale from 0 (no symptoms) to 3 (most symptoms). 24 participants with baseline scores were included in the Montelukast group and 28 participants with baseline scores were included in the ICS group.			
Units: Units on scale			
arithmetic mean	0.45	0.31	
standard deviation	± 0.35	± 0.34	-

Daytime asthma symptom score			
The score is an ordinal scale from 0 (no symptoms) to 5 (most symptoms). 24 participants with baseline scores were included in the Montelukast group and 29 participants with baseline scores were included in the ICS group.			
Units: Units on scale			
arithmetic mean	0.32	0.29	
standard deviation	± 0.42	± 0.4	-
Duration of allergic rhinitis			
24 participants were included in the Montelukast group and 28 participants were included in the ICS group.			
Units: Years			
arithmetic mean	0.4	0.8	
standard deviation	± 0.6	± 1	-
Duration of asthma			
24 participants were included in the Montelukast group and 29 participants were included in the ICS group.			
Units: Years			
arithmetic mean	0.6	1.1	
standard deviation	± 0.7	± 1.2	-

End points

End points reporting groups

Reporting group title	Montelukast

Reporting group description:

Participants were treated for 12 months after randomization: Participants 2 to 5 years of age took one 4 mg chewable tablet and 6 to 14 years of age took one 5 mg chewable tablet daily in the evening. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Reporting group title	Inhaled Corticosteroids (ICS)

Reporting group description:

Participants were treated for 12 months after randomization: Each participant's physician selected the ICS agent, dose, and regimen. If participants had exacerbated from mild to moderate within 12 weeks, ICS was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Subject analysis set title	Daytime Asthma Symptom Score at Baseline - Montelukast
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received study drug and had efficacy measurements both at baseline and during the treatment period. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Subject analysis set title	Daytime Asthma Symptom Score at 12 Weeks - Montelukast
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received study drug and had efficacy measurements both at baseline and during the treatment period. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Subject analysis set title	Daytime Asthma Symptom Score at Baseline - ICS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received study drug and had efficacy measurements both at baseline and during the treatment period. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Subject analysis set title	Daytime Asthma Symptom Score at 12 Weeks - ICS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received study drug and had efficacy measurements both at baseline and during the treatment period. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Subject analysis set title	Daily Allergic Rhinitis Symptom Score at Baseline- Montelukast
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received study drug and had efficacy measurements both at baseline and during the treatment period. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Subject analysis set title	Daily Allergic Rhinitis Symptom Score at 12 Weeks-Montelukast
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received study drug and had efficacy measurements both at baseline and during the treatment period. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were

excluded in the efficacy evaluation at 12 weeks.

Subject analysis set title	Daily Allergic Rhinitis Symptom Score at Baseline - ICS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received study drug and had efficacy measurements both at baseline and during the treatment period. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Subject analysis set title	Daily Allergic Rhinitis Symptom Score 12 Weeks - ICS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received study drug and had efficacy measurements both at baseline and during the treatment period. If participants had exacerbated from mild to moderate within 12 weeks, inhaled corticosteroids (ICS) was added to Montelukast and ICS, respectively and those participants were excluded in the efficacy evaluation at 12 weeks.

Primary: Change from Baseline for Daytime Asthma Symptom Score

End point title	Change from Baseline for Daytime Asthma Symptom Score

End point description:

The score is an ordinal scale from 0 (no symptoms) to 5 (most symptoms). The change was calculated as the score at 12 weeks minus the score at baseline (Statistical Analyses: Change from BL to Week 12 - Montelukast; Change from BL to Week 12 - ICS). Thus, a negative value for change from baseline indicates a favorable outcome. The primary efficacy parameter was a mean change from baseline to treatment for daytime asthma symptom score. Therefore 138 participants who didn't have a daytime asthma symptom score from the participant diary were not included.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Daytime Asthma Symptom Score at Baseline - Montelukast	Daytime Asthma Symptom Score at 12 Weeks - Montelukast	Daytime Asthma Symptom Score at Baseline - ICS	Daytime Asthma Symptom Score at 12 Weeks - ICS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	24	29	29
Units: Units on a scale				
arithmetic mean (standard deviation)	0.32 (± 0.42)	0.16 (± 0.35)	0.29 (± 0.4)	0.13 (± 0.27)

Statistical analyses

Statistical analysis title	Change from BL to Week 12 - Montelukast

Statistical analysis description:

The difference in mean change from baseline to 12 weeks in daytime asthma symptom score was tested by paired t-test (H0: difference =0) for the Montelukast treatment group.

Comparison groups	Daytime Asthma Symptom Score at Baseline - Montelukast v Daytime Asthma Symptom Score at 12 Weeks - Montelukast

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.015
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	-0.03

Notes:

[1] - Subjects in this analysis: N=24 subjects for the within arm (single arm) comparison between BL and Week 12 scores.

Statistical analysis title	Change from BL to Week 12 - ICS

Statistical analysis description:

The difference in mean change from baseline to 12 weeks in daytime asthma symptom score was tested by paired t-test (H0: difference =0) for the ICS treatment group.

Comparison groups	Daytime Asthma Symptom Score at Baseline - ICS v Daytime Asthma Symptom Score at 12 Weeks - ICS
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.027
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.02

Notes:

[2] - Subjects in this analysis: N=29 subjects for the within arm (single arm) comparison between BL and Week 12 scores.

Secondary: Change from Baseline for Daily Allergic Rhinitis Symptom Score

End point title	Change from Baseline for Daily Allergic Rhinitis Symptom Score

End point description:

The score is an ordinal scale from 0 (no symptoms) to 3 (most symptoms). The change was calculated as the score at 12 weeks minus the score at baseline (Statistical Analyses: Change from BL to Week 12 - Montelukast; Change from BL to Week 12 - ICS). Thus, a negative value for change from baseline indicates a favorable outcome. The secondary efficacy parameter was a mean change from baseline to treatment for daily allergic rhinitis symptom score. Therefore 139 participants who didn't have a daily allergic rhinitis symptom score from the participant diary were not included.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Daily Allergic Rhinitis Symptom Score at Baseline- Montelukast	Daily Allergic Rhinitis Symptom Score at 12 Weeks- Montelukast	Daily Allergic Rhinitis Symptom Score at Baseline - ICS	Daily Allergic Rhinitis Symptom Score 12 Weeks - ICS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	24	28	28
Units: Units on a scale				
arithmetic mean (standard deviation)	0.45 (± 0.35)	0.23 (± 0.26)	0.31 (± 0.34)	0.19 (± 0.26)

Statistical analyses

Statistical analysis title	Change from BL to Week 12 - Montelukast

Statistical analysis description:

The difference in mean change from baseline to 12 weeks in daily allergic rhinitis symptom score was tested by paired t-test (H0: difference =0) for the Montelukast treatment group.

Comparison groups	Daily Allergic Rhinitis Symptom Score at Baseline- Montelukast v Daily Allergic Rhinitis Symptom Score at 12 Weeks- Montelukast
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.006
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	-0.07

Notes:

[3] - Subjects in this analysis: N=24 subjects for the within arm (single arm) comparison between BL and Week 12 scores.

Statistical analysis title	Change from BL to Week 12 - ICS

Statistical analysis description:

The difference in mean change from baseline to 12 weeks in daily allergic rhinitis symptom score was tested by paired t-test (H0: difference =0) for the ICS treatment group.

Comparison groups	Daily Allergic Rhinitis Symptom Score at Baseline - ICS v Daily Allergic Rhinitis Symptom Score 12 Weeks - ICS
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.032
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	-0.01

Notes:

[4] - Subjects in this analysis: N=28 subjects for the within arm (single arm) comparison between BL and Week 12 scores.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 12 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Montelukast

Reporting group description:

Participants were treated for 12 months after randomization: Participants 2 to 5 years of age took one 4 mg chewable tablet and 6 to 14 years of age took one 5 mg chewable tablet daily in the evening.

Reporting group title	Inhaled Corticosteroids (ICS)

Reporting group description:

Participants were treated for 12 months after randomization: Each participant's physician selected the ICS agent, dose, and regimen.

Serious adverse events	Montelukast	Inhaled Corticosteroids (ICS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 100 (4.00%)	3 / 91 (3.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 100 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 100 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
VOMITING			
subjects affected / exposed	0 / 100 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	3 / 100 (3.00%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 100 (1.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
CHRONIC SINUSITIS			
subjects affected / exposed	0 / 100 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 100 (1.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Montelukast	Inhaled Corticosteroids (ICS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 100 (83.00%)	70 / 91 (76.92%)	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	9 / 100 (9.00%)	10 / 91 (10.99%)	
occurrences (all)	9	11	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	31 / 100 (31.00%)	24 / 91 (26.37%)	
occurrences (all)	41	34	
Gastrointestinal disorders			
VOMITING			

subjects affected / exposed	6 / 100 (6.00%)	7 / 91 (7.69%)	
occurrences (all)	6	7	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	56 / 100 (56.00%)	47 / 91 (51.65%)	
occurrences (all)	88	92	
DYSPNOEA			
subjects affected / exposed	7 / 100 (7.00%)	5 / 91 (5.49%)	
occurrences (all)	10	6	
NASAL DISCOMFORT			
subjects affected / exposed	15 / 100 (15.00%)	8 / 91 (8.79%)	
occurrences (all)	21	9	
OROPHARYNGEAL PAIN			
subjects affected / exposed	7 / 100 (7.00%)	8 / 91 (8.79%)	
occurrences (all)	8	10	
PRODUCTIVE COUGH			
subjects affected / exposed	12 / 100 (12.00%)	12 / 91 (13.19%)	
occurrences (all)	12	17	
RHINORRHOEA			
subjects affected / exposed	27 / 100 (27.00%)	21 / 91 (23.08%)	
occurrences (all)	36	30	
UPPER AIRWAY OBSTRUCTION			
subjects affected / exposed	30 / 100 (30.00%)	30 / 91 (32.97%)	
occurrences (all)	42	43	
SNEEZING			
subjects affected / exposed	21 / 100 (21.00%)	18 / 91 (19.78%)	
occurrences (all)	29	26	
WHEEZING			
subjects affected / exposed	9 / 100 (9.00%)	13 / 91 (14.29%)	
occurrences (all)	10	15	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	6 / 100 (6.00%)	2 / 91 (2.20%)	
occurrences (all)	6	2	
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed occurrences (all)	9 / 100 (9.00%) 9	7 / 91 (7.69%) 10	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This was an open-label study. Only 53 patients had diary information with daytime asthma symptom score - thus, 138 cases were dropped from analysis due to lack of daytime asthma symptom score.

Notes: