Clinical trial results:
A Phase III, Open-Label Clinical Trial to Study the Safety and Pharmacokinetics of MK-0476 in Japanese Pediatric Subjects Aged 1 to 15 Years Old with Perennial Allergic Rhinitis

Summary

EudraCT number	2014-004871-22
Trial protocol	Outside EU/EEA
Global end of trial date	24 December 2013

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	0476-520

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01852812
WHO universal trial number (UTN)	-
Other trial identifiers	MK-0476-520: Merck protocol number

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 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 December 2013
Global end of trial reached?	Yes
Global end of trial date	24 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the safety and pharmacokinetics of montelukast (MK-0476) in the treatment of Japanese pediatric participants with perennial allergic rhinitis (PAR). The primary hypothesis of this study is that montelukast oral granules (OG) and chewable tablets (CT) provide appropriate exposure to montelukast in Japanese pediatric participants with PAR.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 June 2013
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	Japan: 87
Worldwide total number of subjects	87
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)	81
Adolescents (12-17 years)	6
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:

Japanese participants aged 1 to 15 years who had perennial allergic rhinitis (PAR) were screened for this study.

Period 1

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

Blinding implementation details:

No blinding was used in this open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Montelukast 4 mg OG/1-5 year olds

Arm description:

Participants receive montelukast 4 mg oral granules (OG) in one sachet orally (PO) once daily (QD) at bed time for 4 weeks with an option to continue for an additional 8 weeks (12 weeks total)

Arm type	Experimental
Investigational medicinal product name	Montelukast Oral Granules
Investigational medicinal product code	
Other name	MK-0475
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Montelukast 4 mg oral granules in one sachet once daily at bedtime for up to 12 weeks

Arm title	Montelukast 5 mg CT/6-9 year olds

Arm description:

Participants receive montelukast 5 mg chewable tablets (CT) in one tablet PO QD at bed time for 12 weeks

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

Dosage and administration details:

Montelukast 5 mg chewable tablets once daily at bedtime for up to 12 weeks

Arm title	Montelukast 5 mg CT/10-15 year olds

Arm description:

Participants receive montelukast 5 mg CT in one tablet PO QD at bed time for 12 weeks

Arm type	Experimental

Investigational medicinal product name	Montelukast Chewable Tablets
Investigational medicinal product code	
Other name	MK-0476
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast 5 mg chewable tablets once daily at bedtime for up to 12 weeks

Number of subjects in period 1	Montelukast 4 mg OG/1-5 year olds	Montelukast 5 mg CT/6-9 year olds	Montelukast 5 mg CT/10-15 year olds
Started	51	18	18
Completed	51	17	17
Not completed	0	1	1
Adverse event, non-fatal	-	-	1
Non-compliance with study drug	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Montelukast 4 mg OG/1-5 year olds
Reporting group description:	
Participants receive montelukast 4 mg oral granules (OG) in one sachet orally (PO) once daily (QD) at bed time for 4 weeks with an option to continue for an additional 8 weeks (12 weeks total)	
Reporting group title	Montelukast 5 mg CT/6-9 year olds
Reporting group description:	
Participants receive montelukast 5 mg chewable tablets (CT) in one tablet PO QD at bed time for 12 weeks	
Reporting group title	Montelukast 5 mg CT/10-15 year olds
Reporting group description:	
Participants receive montelukast 5 mg CT in one tablet PO QD at bed time for 12 weeks	

Reporting group values	Montelukast 4 mg OG/1-5 year olds	Montelukast 5 mg CT/6-9 year olds	Montelukast 5 mg CT/10-15 year olds
Number of subjects	51	18	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	51	18	12
Adolescents (12-17 years)	0	0	6
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	3.6	7.8	11.3
standard deviation	± 1.4	± 1.3	± 1
Gender, Male/Female Units: Participants			
Female	24	8	5
Male	27	10	13

Reporting group values	Total		
Number of subjects	87		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	81		

Adolescents (12-17 years)	6		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Participants			
Female	37		
Male	50		

Subject analysis sets

Subject analysis set title	Montelukast 5 mg CT/6-15 year olds
Subject analysis set type	Full analysis

Subject analysis set description:

Participants receive montelukast 5 mg CT in one tablet PO QD at bed time for 12 weeks

Reporting group values	Montelukast 5 mg CT/6-15 year olds		
Number of subjects	36		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	30		
Adolescents (12-17 years)	6		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	±		
Gender, Male/Female			
Units: Participants			
Female			
Male			

End points

End points reporting groups

Reporting group title	Montelukast 4 mg OG/1-5 year olds
Reporting group description:	
Participants receive montelukast 4 mg oral granules (OG) in one sachet orally (PO) once daily (QD) at bed time for 4 weeks with an option to continue for an additional 8 weeks (12 weeks total)	
Reporting group title	Montelukast 5 mg CT/6-9 year olds
Reporting group description:	
Participants receive montelukast 5 mg chewable tablets (CT) in one tablet PO QD at bed time for 12 weeks	
Reporting group title	Montelukast 5 mg CT/10-15 year olds
Reporting group description:	
Participants receive montelukast 5 mg CT in one tablet PO QD at bed time for 12 weeks	
Subject analysis set title	Montelukast 5 mg CT/6-15 year olds
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants receive montelukast 5 mg CT in one tablet PO QD at bed time for 12 weeks	

Primary: Percentage of Participants Who Experience at Least One Adverse Event (AE)

End point title	Percentage of Participants Who Experience at Least One Adverse Event (AE)[1][2]
End point description:	
An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of study drug or protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a pre-existing condition that is temporally associated with the use of study drug is also an AE. Participants were monitored for the occurrence of AEs for up to 14 days after last dose of study drug (up to a total of 14 weeks). AEs were reported based on the dose of study drug participants received.	
End point type	Primary
End point timeframe:	
Up to 14 days after last dose of study drug (Up to 14 weeks)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this end point.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety data from the two montelukast 5 mg CT groups (6-9 year olds and 10-15 year olds) were pooled for safety analyses.

End point values	Montelukast 4 mg OG/1-5 year olds	Montelukast 5 mg CT/6-15 year olds		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51[3]	36[4]		
Units: Percentage of participants				
number (not applicable)	74.5	55.6		

Notes:

[3] - All randomized participants who received ≥1 dose of study drug.

[4] - All randomized participants who received ≥1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Discontinue Study Drug Due to an AE

End point title	Percentage of Participants Who Discontinue Study Drug Due to an AE[5][6]

End point description:

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of study drug or protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a pre-existing condition that is temporally associated with the use of study drug is also an AE. Discontinuations due to an AE were reported based on the dose of study drug participants received.

End point type	Primary

End point timeframe:

Up to 12 weeks

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this end point.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety data from the two montelukast 5 mg CT groups (6-9 year olds and 10-15 year olds) were pooled for safety analyses.

End point values	Montelukast 4 mg OG/1-5 year olds	Montelukast 5 mg CT/6-15 year olds		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	51[7]	36[8]		
Units: Percentage of participants				
number (not applicable)	0	2.8		

Notes:

[7] - All randomized participants who received ≥1 dose of study drug.

[8] - All randomized participants who received ≥1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Time-Concentration Curve (AUC 0-∞) of Montelukast CT and Montelukast OG

End point title	Area Under the Time-Concentration Curve (AUC 0-∞) of Montelukast CT and Montelukast OG[9]

End point description:

Blood samples for pharmacokinetic (PK) assessments were collected at either 1 hour (h) or 3 h post-dose on Day 1 and at either 14 h or 22 h post-dose on Day 28.

End point type	Primary

End point timeframe:

Up to Day 28 after first dose of study drug

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this end point.

End point values	Montelukast 4 mg OG/1-5 year olds	Montelukast 5 mg CT/6-9 year olds	Montelukast 5 mg CT/10-15 year olds	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51[10]	18[11]	18[12]	
Units: h*ng/mL				
arithmetic mean (standard deviation)	4300 (± 890)	4350 (± 760)	3500 (± 620)	

Notes:

[10] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.
[11] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.
[12] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) of Montelukast CT and Montelukast OG

End point title	Maximum Plasma Concentration (Cmax) of Montelukast CT and Montelukast OG[13]

End point description:

Blood samples for PK assessments were collected at either 1 h or 3 h post-dose on Day 1 and at either 14 h or 22 h post-dose on Day 28.

End point type	Primary

End point timeframe:

Up to Day 28 after first dose of study drug

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this end point.

End point values	Montelukast 4 mg OG/1-5 year olds	Montelukast 5 mg CT/6-9 year olds	Montelukast 5 mg CT/10-15 year olds	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51[14]	18[15]	18[16]	
Units: ng/mL				
arithmetic mean (standard deviation)	510 (± 84)	438 (± 82)	344 (± 61)	

Notes:

[14] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.
[15] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.
[16] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.

Statistical analyses

No statistical analyses for this end point

Primary: Time to Cmax (Tmax) of Montelukast CT and Montelukast OG

End point title	Time to Cmax (Tmax) of Montelukast CT and Montelukast

End point description:

Blood samples for PK assessments were collected at either 1 h or 3 h post-dose on Day 1 and at either

14 h or 22 h post-dose on Day 28.

End point type	Primary

End point timeframe:

Up to Day 28 after first dose of study drug

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this end point.

End point values	Montelukast 4 mg OG/1-5 year olds	Montelukast 5 mg CT/6-9 year olds	Montelukast 5 mg CT/10-15 year olds	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51[18]	18[19]	18[20]	
Units: Hours				
arithmetic mean (standard deviation)	2.74 (± 0.6)	3.55 (± 0.71)	3.65 (± 0.6)	

Notes:

[18] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.
[19] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.
[20] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Elimination Half-life (t1/2) of Montelukast CT and Montelukast OG

End point title	Apparent Elimination Half-life (t1/2) of Montelukast CT and Montelukast OG[21]

End point description:

Blood samples for PK assessments were collected at either 1 h or 3 h post-dose on Day 1 and at either 14 h or 22 h post-dose on Day 28.

End point type	Primary

End point timeframe:

Up to Day 28 after first dose of study drug

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this end point.

End point values	Montelukast 4 mg OG/1-5 year olds	Montelukast 5 mg CT/6-9 year olds	Montelukast 5 mg CT/10-15 year olds	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51[22]	18[23]	18[24]	
Units: Hours				
arithmetic mean (standard deviation)	1.27 (± 0.56)	2.01 (± 0.75)	2.08 (± 0.66)	

Notes:

[22] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.
[23] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol violations.
[24] - All participants who received ≥1 dose of study drug, had ≥1 PK assessment & no protocol

violations.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 days after last dose of study drug (Up to 14 weeks)

Adverse event reporting additional description:

The safety population consisted of all participants who received at least one dose of study drug. AEs were reported based on the dose of study drug participants received. Data from the two montelukast 5 mg CT groups (6-9 year olds and 10-15 year olds) were pooled for safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Montelukast 5 mg CT/6-15 year olds

Reporting group description:

Participants receive montelukast 5 mg CT in one tablet PO QD at bed time for 12 weeks

Reporting group title	Montelukast 4 mg OG/1-5 year olds

Reporting group description:

Participants receive montelukast 4 mg OG in one sachet PO QD at bed time for 4 weeks with an option to continue for an additional 8 weeks (12 weeks total)

Serious adverse events	Montelukast 5 mg CT/6-15 year olds	Montelukast 4 mg OG/1-5 year olds	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	0 / 51 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Montelukast 5 mg CT/6-15 year olds	Montelukast 4 mg OG/1-5 year olds	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 36 (50.00%)	37 / 51 (72.55%)	
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	2 / 36 (5.56%)	2 / 51 (3.92%)	
occurrences (all)	4	2	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 36 (0.00%)	4 / 51 (7.84%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Miliaria			
subjects affected / exposed	2 / 36 (5.56%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 36 (0.00%)	6 / 51 (11.76%)	
occurrences (all)	0	8	
Bronchitis			
subjects affected / exposed	3 / 36 (8.33%)	3 / 51 (5.88%)	
occurrences (all)	3	4	
Gastroenteritis			
subjects affected / exposed	1 / 36 (2.78%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 36 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	12 / 36 (33.33%)	22 / 51 (43.14%)	
occurrences (all)	15	32	
Otitis media			
subjects affected / exposed	1 / 36 (2.78%)	4 / 51 (7.84%)	
occurrences (all)	1	4	
Otitis media acute			
subjects affected / exposed	0 / 36 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	4	
Pharyngitis			
subjects affected / exposed	3 / 36 (8.33%)	9 / 51 (17.65%)	
occurrences (all)	4	14	

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