Clinical trial results:
A Double-Blind, Randomized, Placebo-Controlled, Multicenter, Crossover Study of MK-1029 in Adult Subjects with Persistent Asthma Who Remain Uncontrolled While Being Maintained on Montelukast

Summary

EudraCT number	2012-000642-35
Trial protocol	DE
Global end of trial date	05 May 2014

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	02 May 2015

Trial information

Trial identification

Sponsor protocol code	MK-1029-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01624974
WHO universal trial number (UTN)	-
Other trial identifiers	MK-1029-011: 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2014
Global end of trial reached?	Yes
Global end of trial date	05 May 2014
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 the efficacy and safety of MK-1029+montelukast, compared with placebo+montelukast, in participants aged 18 to 75 years (changed to 65 years with protocol amendment 02) with evidence of asthma uncontrolled on montelukast, using measures of lung function (forced expiratory volume in 1 second [FEV1], peak expiratory flow [PEF]) and participant-reported end points, including symptoms, short-acting β-agonist (SABA) use and Asthma Control Questionnaire responses (percentage of days with asthma exacerbations). The primary objective is to demonstrate that MK-1029+montelukast, compared with placebo+montelukast, results in improvement in FEV1 after 4 weeks of treatment with MK-1029+montelukast.

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: subjects were permitted to use investigator-supplied inhaled SABA (albuterol or salbutamol) throughout the study on an "as-needed" basis for relief of asthma symptoms.

Background therapy:

Subjects were permitted to use investigator-supplied inhaled SABA (albuterol or salbutamol) throughout the study on an "as-needed" basis for relief of asthma symptoms.

Evidence for comparator: -

Actual start date of recruitment	09 August 2012
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	Germany: 21
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Colombia: 11
Country: Number of subjects enrolled	Guatemala: 26
Country: Number of subjects enrolled	Peru: 27
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	115
EEA total number of subjects	21

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	112
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were aged 18 to 65 years, had persistent asthma that remained uncontrolled while being maintained on montelukast, demonstrated reversibility of airway obstruction defined as an increase in FEV1 of ≥12% after SABA administration and ≥200 mL, and had an FEV1 of ≥55% and ≤85% of the predicted value.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MK-1029 150 mg+Montelukast then Placebo+Montelukast

Arm description:

Treatment Period 1: Participants received MK-1029 150 mg administered orally (PO) once daily (QD) in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Arm type	Experimental
Investigational medicinal product name	MK-1029
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MK-1029 150 mg tablet administered PO QD in the evening for 4 weeks

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast 10 mg tablet administered PO QD in the evening for 4 weeks

Arm title	Placebo+Montelukast then MK-1029 150 mg+Montelukast

Arm description:

Treatment Period 1: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received MK-1029 150 mg administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Arm type	Active comparator

Investigational medicinal product name	Placebo to MK-1029
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet administered PO QD in the evening for 4 weeks

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast 10 mg tablet administered PO QD in the evening for 4 weeks

Number of subjects in period 1	MK-1029 150 mg+Montelukast then Placebo+Montelukast	Placebo+Montelukast then MK-1029 150 mg+Montelukast
Started	59	56
Treated	54	53
Completed	47	45
Not completed	12	11
Physician decision	5	3
Randomization error, not treated	5	3
Adverse event, non-fatal	-	1
Noncompliance with protocol	1	2
Protocol deviation	1	-
Lack of efficacy	-	2

Period 2

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

Arms

Are arms mutually exclusive?	Yes

Arm title	MK-1029 150 mg+Montelukast then Placebo+Montelukast

Arm description:

Treatment Period 1: Participants received MK-1029 150 mg administered orally (PO) once daily (QD) in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Arm type	Experimental
Investigational medicinal product name	MK-1029
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MK-1029 150 mg tablet administered PO QD in the evening for 4 weeks

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast 10 mg tablet administered PO QD in the evening for 4 weeks

Arm title	Placebo+Montelukast then MK-1029 150 mg+Montelukast

Arm description:

Treatment Period 1: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received MK-1029 150 mg administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Arm type	Active comparator
Investigational medicinal product name	Placebo to MK-1029
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet administered PO QD in the evening for 4 weeks

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast 10 mg tablet administered PO QD in the evening for 4 weeks

Number of subjects in period 2	MK-1029 150 mg+Montelukast then Placebo+Montelukast	Placebo+Montelukast then MK-1029 150 mg+Montelukast
Started	47	45
Completed	44	42
Not completed	3	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	-
Noncompliance with protocol	-	1
Lack of efficacy	1	1

Period 3

Period 3 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	MK-1029 150 mg+Montelukast then Placebo+Montelukast

Arm description:

Treatment Period 1: Participants received MK-1029 150 mg administered orally (PO) once daily (QD) in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Arm type	Experimental
Investigational medicinal product name	MK-1029
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MK-1029 150 mg tablet administered PO QD in the evening for 4 weeks

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast 10 mg tablet administered PO QD in the evening for 4 weeks

Arm title	Placebo+Montelukast then MK-1029 150 mg+Montelukast

Arm description:

Treatment Period 1: Participants received placebo to MK-1029 PO QD in the evening plus montelukast

10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received MK-1029 150 mg administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Arm type	Active comparator
Investigational medicinal product name	Placebo to MK-1029
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet administered PO QD in the evening for 4 weeks

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Montelukast 10 mg tablet administered PO QD in the evening for 4 weeks

Number of subjects in period 3	MK-1029 150 mg+Montelukast then Placebo+Montelukast	Placebo+Montelukast then MK-1029 150 mg+Montelukast
Started	44	42
Completed	39	42
Not completed	5	0
Physician decision	3	-
Adverse event, non-fatal	1	-
Lack of efficacy	1	-

Baseline characteristics

Reporting groups

Reporting group title	MK-1029 150 mg+Montelukast then Placebo+Montelukast

Reporting group description:

Treatment Period 1: Participants received MK-1029 150 mg administered orally (PO) once daily (QD) in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Reporting group title	Placebo+Montelukast then MK-1029 150 mg+Montelukast

Reporting group description:

Treatment Period 1: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received MK-1029 150 mg administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Reporting group values	MK-1029 150 mg+Montelukast then Placebo+Montelukast	Placebo+Montelukast then MK-1029 150 mg+Montelukast	Total
Number of subjects	59	56	115
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	58	54	112
From 65-84 years	1	2	3
85 years and over	0	0	0
Gender categorical Units: Subjects			
Male	19	16	35
Female	40	40	80

End points

End points reporting groups

Reporting group title	MK-1029 150 mg+Montelukast then Placebo+Montelukast

Reporting group description:

Treatment Period 1: Participants received MK-1029 150 mg administered orally (PO) once daily (QD) in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Reporting group title	Placebo+Montelukast then MK-1029 150 mg+Montelukast

Reporting group description:

Treatment Period 1: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received MK-1029 150 mg administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Reporting group title	MK-1029 150 mg+Montelukast then Placebo+Montelukast

Reporting group description:

Treatment Period 1: Participants received MK-1029 150 mg administered orally (PO) once daily (QD) in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Reporting group title	Placebo+Montelukast then MK-1029 150 mg+Montelukast

Reporting group description:

Treatment Period 1: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received MK-1029 150 mg administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Reporting group title	MK-1029 150 mg+Montelukast then Placebo+Montelukast

Reporting group description:

Treatment Period 1: Participants received MK-1029 150 mg administered orally (PO) once daily (QD) in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Reporting group title	Placebo+Montelukast then MK-1029 150 mg+Montelukast

Reporting group description:

Treatment Period 1: Participants received placebo to MK-1029 PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Period 2: Participants received MK-1029 150 mg administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks. Treatment Periods 1 and 2 were separated by a 4-week washout period during which participants received placebo to MK-1029 plus montelukast 10 mg.

Subject analysis set title	MK-1029 150 mg+Montelukast
Subject analysis set type	Full analysis

Subject analysis set description:

The analysis set consists of all participants who received at least one dose of study drug in any of the crossover periods and had at least one measurement for the analysis end point (pre-dose baseline or post-randomization observation).

Subject analysis set title	Placebo+Montelukast
Subject analysis set type	Full analysis

Subject analysis set description:

The analysis set consists of all participants who received at least one dose of study drug in any of the crossover periods and had at least one measurement for the analysis end point (pre-dose baseline or post-randomization observation).

Primary: Change from Baseline in FEV1

End point title	Change from Baseline in FEV1

End point description:

FEV1 is the measurement, in liters, of the amount of air exhaled in the first second of forced exhalation. At each study visit, participant FEV1 was measured in triplicate, with the largest FEV1 being recorded. The end point was based on spirometry performed at each site visit. Two baseline values were established for the analysis of this crossover study. The baseline value for the first treatment period was obtained at Week 0. The baseline value for the second treatment period was obtained at Week 8. The ending value for each treatment period was obtained at the end of the fourth week of each 4-week treatment period.

End point type	Primary

End point timeframe:

Baseline and Week 4 of each Treatment Period

End point values	MK-1029 150 mg+Montelukast	Placebo+Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[1]	97[2]		
Units: liters				
least squares mean (confidence interval 95%)	0.065 (0.003 to 0.126)	0.017 (-0.044 to 0.078)		

Notes:

[1] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

[2] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

Statistical analyses

Statistical analysis title	Difference in Changes from Baseline in FEV1

Statistical analysis description:

The difference in least squares (LS) means of change from baseline in FEV1 (MK-1029 150 mg+Montelukast compared to Placebo+Montelukast) was estimated using a longitudinal data analysis (LDA) model with FEV1 obtained at baseline, Week 2 and Week 4 as response. Model included treatment, visit, period and treatment-by-visit interactions as fixed effects and participant as random effect. The unstructured covariance matrix was used to model the correlation among repeated measurements.

Comparison groups	MK-1029 150 mg+Montelukast v Placebo+Montelukast
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.282
Method	LDA model
Parameter estimate	Difference in LS means
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.039
upper limit	0.134

Secondary: Change from Baseline in Daytime Symptom Score (DSS)

End point title	Change from Baseline in Daytime Symptom Score (DSS)

End point description:

In the evening just before going to bed, participants scored their asthma symptoms for the period since arising by answering the following 4 questions in eDiaries: 1) How often did you experience asthma symptoms today?, 2) How much did your asthma symptoms bother you?, 3) How much activity could you do today? and 4) How often did your asthma affect your activities today? The 4 questions were evaluated on a 7-point scale (0=best to 6=worst). The endpoint was calculated based on the eDiary entries as the average of the 4 questions about asthma symptoms (end point range: 0=best to 6=worst). Two baseline values were established for the analysis of this crossover study. The baseline value for the first treatment period was based on the 7-day period prior to Week 0. The baseline value for the second treatment period was based on the 7-day period prior to Week 8. The ending value in a treatment period was calculated as the average DSS over the last week of a 4-week treatment period.

End point type	Secondary

End point timeframe:

Baseline and Week 4 of each Treatment Period

End point values	MK-1029 150 mg+Montelukast	Placebo+Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91[3]	96[4]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.18 (-0.34 to -0.03)	-0.09 (-0.24 to 0.06)		

Notes:

[3] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

[4] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

Statistical analyses

Statistical analysis title	Difference in Changes from Baseline in DSS

Statistical analysis description:

The difference in LS means of change from baseline in DSS (MK-1029 150 mg+Montelukast compared to Placebo+Montelukast) was estimated using a LDA model with DSS obtained at Baseline, Week 2 and Week 4 as response. The model included treatment, visit, period and treatment-by-visit interaction as fixed effects and participant as random effect. The unstructured covariance matrix was used to model the correlation among repeated measurements.

Comparison groups	MK-1029 150 mg+Montelukast v Placebo+Montelukast
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.381
Method	LDA model
Parameter estimate	Difference in LS means
Point estimate	-0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.12

Secondary: Change from Baseline in Use of Short-acting ß-agonist (SABA)

End point title	Change from Baseline in Use of Short-acting ß-agonist (SABA)

End point description:

Twice daily (upon arising and before going to sleep), participants recorded the total number of puffs (actuations) of SABA used for asthma symptoms in their eDiaries. This end point was defined as the number of SABA puffs used in one day and was calculated based on eDiary entries as the sum of daytime and nighttime number of puffs of SABA. Two baseline values were established for the analysis of this crossover study. The baseline value for the first treatment period was based on the 7-day period prior to Week 0. The baseline value for the second treatment period was based on the 7-day period prior to Week 8. The ending value in a treatment period was calculated as the average number of SABA puffs used in one day over the last week of a 4-week treatment period.

End point type	Secondary

End point timeframe:

Baseline and Week 4 of each Treatment Period

End point values	MK-1029 150 mg+Montelukast	Placebo+Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94[5]	98[6]		
Units: puffs				
least squares mean (confidence interval 95%)	-0.648 (-1.059 to -0.236)	-0.538 (-0.933 to -0.143)		

Notes:

[5] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

[6] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

Statistical analyses

Statistical analysis title	Difference in Changes from Baseline in SABA Use

Statistical analysis description:

The difference in LS means of change from baseline in SABA use (MK-1029 150 mg+Montelukast compared to Placebo+Montelukast) was estimated using a LDA model with SABA use (puffs) obtained at Baseline, Week 2 and Week 4 as response. The model included treatment, visit, period and treatment-by-visit interaction as fixed effects and participant as random effect. The unstructured covariance matrix was used to model the correlation among repeated measurements.

Comparison groups	MK-1029 150 mg+Montelukast v Placebo+Montelukast

Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.704
Method	LDA model
Parameter estimate	Difference in LS means
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.679
upper limit	0.46

Secondary: Change from Baseline in Number of Nocturnal Awakenings

End point title	Change from Baseline in Number of Nocturnal Awakenings

End point description:

This end point was defined as the total number of nights a participant awakened with asthma. The end point was calculated based on eDiary entries by dividing the number of nights a participant awakened with asthma (positive responses of once, more than once, awake "all night") by the total number of nights (all responses) and then multiplying by 7 (standardized to a 7-day period). Two baseline values were established for the analysis of this crossover study. The baseline value for the first treatment period was based on the 7-day period prior to Week 0. The baseline value for the second treatment period was based on the 7-day period prior to Week 8. The ending value in a treatment period was calculated as the average number of nights awake over the last week of a 4-week treatment period.

End point type	Secondary

End point timeframe:

Baseline and Week 4 of each Treatment Period

End point values	MK-1029 150 mg+Montelukast	Placebo+Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	69[7]	74[8]		
Units: number of nights awake				
least squares mean (confidence interval 95%)	-0.98 (-1.64 to -0.33)	-0.91 (-1.53 to -0.28)		

Notes:

[7] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

[8] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

Statistical analyses

Statistical analysis title	Difference in Changes in Nocturnal Awakenings

Statistical analysis description:

The difference in LS means of change from baseline in number of nights awake (MK-1029 150 mg+Montelukast compared to Placebo+Montelukast) was estimated using a LDA model with number of nights awake obtained at Baseline, Week 2 and Week 4 as response. The model included treatment, visit, period and treatment-by-visit interaction as fixed effects and participant as random effect. The unstructured covariance matrix was used to model the correlation among repeated measurements.

Comparison groups	MK-1029 150 mg+Montelukast v Placebo+Montelukast
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.866
Method	LDA model
Parameter estimate	Difference in LS means
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	0.82

Secondary: Change from Baseline in Morning Peak Expiratory Flow (PEF)

End point title	Change from Baseline in Morning Peak Expiratory Flow (PEF)

End point description:

A peak flow meter was provided to all participants for the measurement of PEF in liters/minute at home. Participants performed triplicate PEF measurements in the morning upon arising. All 3 values were to be recorded in the eDiaries; the best value was determined through the eDiaries. The end point was calculated based on eDiary entries. Two baseline values were established for the analysis of this crossover study. The baseline value for the first treatment period was based on the 7-day period prior to Week 0. The baseline value for the second treatment period was based on the 7-day period prior to Week 8. The ending value in a treatment period was calculated as the average morning PEF over the last week of a 4-week treatment period.

End point type	Secondary

End point timeframe:

Baseline and Week 4 of each Treatment Period

End point values	MK-1029 150 mg+Montelukast	Placebo+Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93[9]	98[10]		
Units: liters/minute				
least squares mean (confidence interval 95%)	6.55 (-1.66 to 14.75)	-3.42 (-11.54 to 4.71)		

Notes:

[9] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

[10] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

Statistical analyses

Statistical analysis title	Difference in Changes from Baseline in Morning PEF

Statistical analysis description:

The difference in LS means of change from baseline in morning PEF (MK-1029 150 mg+Montelukast compared to Placebo+Montelukast) was estimated using a LDA model with morning PEF (L/min) obtained at Baseline, Week 2 and Week 4 as response. The model included treatment, visit, period and treatment-by-visit interaction as fixed effects and participant as random effect. The unstructured

covariance matrix was used to model the correlation among repeated measurements.

Comparison groups	MK-1029 150 mg+Montelukast v Placebo+Montelukast
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	LDA model
Parameter estimate	Difference in LS means
Point estimate	9.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.58
upper limit	21.5

Secondary: Change from Baseline in Nighttime PEF

End point title	Change from Baseline in Nighttime PEF

End point description:

A peak flow meter was provided to all participants for the measurement of PEF in liters/minute at home. Participants performed triplicate PEF measurements at night, immediately before study drug adminstration, at bedtime. All 3 values were to be recorded in the eDiaries; the best value was determined through the eDiaries. The end point was calculated based on eDiary entries. Two baseline values were established for the analysis of this crossover study. The baseline value for the first treatment period was based on the 7-day period prior to Week 0. The baseline value for the second treatment period was based on the 7-day period prior to Week 8. The ending value in a treatment period was calculated as the average nighttime PEF over the last week of a 4-week treatment period.

End point type	Secondary

End point timeframe:

Baseline and Week 4 of each Treatment Period

End point values	MK-1029 150 mg+Montelukast	Placebo+Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91[11]	96[12]		
Units: liters/minute				
least squares mean (confidence interval 95%)	7.51 (-0.81 to 15.83)	-4.31 (-12.49 to 3.87)		

Notes:

[11] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

[12] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

Statistical analyses

Statistical analysis title	Difference in Changes in Nighttime PEF

Statistical analysis description:

The difference in LS means of change from baseline in nighttime PEF (MK-1029 150 mg+Montelukast compared to Placebo+Montelukast) was estimated using a LDA model with nighttime PEF (L/min) obtained at Baseline, Week 2 and Week 4 as response. The model included treatment, visit, period and

treatment-by-visit interaction as fixed effects and participant as random effect. The unstructured covariance matrix was used to model the correlation among repeated measurements.

Comparison groups	MK-1029 150 mg+Montelukast v Placebo+Montelukast
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	LDA model
Parameter estimate	Difference in LS means
Point estimate	11.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	23.48

Secondary: Change from Baseline in Asthma Control Questionnaire (ACQ) Score

End point title	Change from Baseline in Asthma Control Questionnaire (ACQ) Score

End point description:

Participants were asked to answer 6 questions about their asthma control over the previous week: 1) How often were you woken by your asthma during the night? 2) How bad were your asthma symptoms when you woke up in the morning? 3) How limited were you in your activities because of your asthma? 4) How much shortness of breath did you experience because of your asthma? 5) How much of the time did you wheeze? and 6) How many puffs/inhalations of SABA bronchodilator have you used each day? The AQC is scored as the mean of the responses to the 6 questions (score range: 0=totally controlled to 6=extremely poorly controlled). Two baseline values were established for this analysis. The baseline value for the first treatment period was obtained at Week 0. The baseline value for the second treatment period was obtained at Week 8. The ending value in a 4-week treatment period was participant responses at Week 4 of each treatment period.

End point type	Secondary

End point timeframe:

Baseline and Week 4 of each Treatment Period

End point values	MK-1029 150 mg+Montelukast	Placebo+Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97[13]	99[14]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.54 (-0.74 to -0.35)	-0.5 (-0.69 to -0.3)		

Notes:

[13] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

[14] - Participants who took ≥1 dose of study drug in any treatment period and had ≥1 end point measurement

Statistical analyses

Statistical analysis title	Difference in Changes from Baseline in ACQ Score

Statistical analysis description:

The difference in LS means of change from baseline in ACQ score (MK-1029 150 mg+Montelukast compared to Placebo+Montelukast) was estimated using a LDA model with ACQ score obtained at Baseline and Week 4 as response. The model included treatment, visit, period and treatment-by-visit interaction as fixed effects and participant as random effect. The unstructured covariance matrix was used to model the correlation among repeated measurements.

Comparison groups	MK-1029 150 mg+Montelukast v Placebo+Montelukast
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746
Method	LDA model
Parameter estimate	Difference in LS means
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.23

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 2 weeks after last dose of study drug in a treatment period (Up to 14 weeks)

Adverse event reporting additional description:

Population includes all randomized participants who received ≥1 dose of study drug. Participants are included in the treatment corresponding to the study drug they actually received. A given participant can be counted under both treatment arms if the participant experienced adverse events in both treatment periods.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo + Montelukast

Reporting group description:

The reporting group consists of participants who received at least one dose of placebo plus montelukast in at least one of the two treatment periods. Participants were to receive placebo administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks.

Reporting group title	MK-1029 150 mg + Montelukast

Reporting group description:

The reporting group consists of participants who received at least one dose of MK-1029 150 mg plus montelukast in at least one of the two treatment periods. Participants were to receive MK-1029 150 mg administered PO QD in the evening plus montelukast 10 mg PO QD in the evening for 4 weeks.

Serious adverse events	Placebo + Montelukast	MK-1029 150 mg + Montelukast	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 97 (0.00%)	0 / 96 (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	Placebo + Montelukast	MK-1029 150 mg + Montelukast	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 97 (14.43%)	14 / 96 (14.58%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	9 / 97 (9.28%)	7 / 96 (7.29%)	
occurrences (all)	10	7	

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 8	8 / 96 (8.33%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2012	Amendment 01: The major reasons for this amendment were (1) to note changes in the inclusion criteria to allow for participants on oral controllers to participate in the trial; (2) to specify that the list of excluded medications included strong inhibitors, or substrates, of organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3, to modify the list, and to indicate that the list provided was not exclusive; and (3) to insert flexible language allowing investigators to administer between 2 and 4 puffs of albuterol/salbutamol for reversibility testing and to maintain flexible language throughout the protocol.
01 March 2013	Amendment 02: The primary reason for this amendment was to conform with requests by regulatory authorities, to note changes to the inclusion criteria related to age range (changed to 18 to 65 years of age), FEV1 predicted values for participants on controllers, and participant treatment categories. In addition, the definition of the T helper cell type 2 (Th2)-high participant on controllers was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported