Clinical trial results:
MK-476 IV formulation Phase III Open Label Exploratory Comparative Study - Acute Exacerbations of Asthma -

Summary

EudraCT number	2014-004749-28
Trial protocol	Outside EU/EEA
Global end of trial date	01 August 2007

Results information

Result version number	v1
This version publication date	13 June 2016
First version publication date	19 July 2015

Trial information

Trial identification

Sponsor protocol code	MK-0476-334

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00442338
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	01 August 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2007
Global end of trial reached?	Yes
Global end of trial date	01 August 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study estimates the efficacy and safety of MK-0476 and aminophylline intravenous (IV) administration in adult participants with acute 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 measures defined for this individual study were in place for the protection of trial subjects: as needed administration of beta agonists, IV drip corticosteroids, and oxygen therapy during the treatment period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 2007
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: 91
Worldwide total number of subjects	91
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)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	57
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase III. Studied period: March 12, 2007 (date study drug was first administered to first participant) to August 1, 2007 (date study drug was last administered to last participant). Study was conducted at 31 clinical sites in Japan.

Pre-assignment

Screening details:

Participants with acute exacerbation of bronchial asthma received standard treatments of inhaled β-agonist or oxygen inhalation to treat the acute exacerbations during the 60 minutes in the screening period before the study randomization. Additional inclusion and exclusion criteria applied.

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 7 mg

Arm description:

Montelukast 7 mg IV administration

Arm type	Experimental
Investigational medicinal product name	montelukast sodium
Investigational medicinal product code	
Other name	MK-0476
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Montelukast 7 mg single injection (IV bolus administration) over 2-3 minutes

Arm title	Montelukast 14 mg

Arm description:

Montelukast 14 mg IV administration

Arm type	Experimental
Investigational medicinal product name	montelukast sodium
Investigational medicinal product code	
Other name	MK-0476
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Montelukast 14 mg single injection (IV bolus administration) over 5 minutes

Arm title	Aminophylline 250 mg

Arm description:

Aminophylline 250 mg IV drip administration

Arm type	Active comparator

Investigational medicinal product name	aminophylline hydrate
Investigational medicinal product code	
Other name	Kyophyllin® Injection 2.5%, FK05
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Aminophylline 250 mg IV drip infusion over 60 minutes

Number of subjects in period 1	Montelukast 7 mg	Montelukast 14 mg	Aminophylline 250 mg
Started	30	30	31
Completed	30	30	31

Baseline characteristics

Reporting groups	
Reporting group title	Montelukast 7 mg
Reporting group description: Montelukast 7 mg IV administration	
Reporting group title	Montelukast 14 mg
Reporting group description: Montelukast 14 mg IV administration	
Reporting group title	Aminophylline 250 mg
Reporting group description: Aminophylline 250 mg IV drip administration	

Reporting group values	Montelukast 7 mg	Montelukast 14 mg	Aminophylline 250 mg
Number of subjects	30	30	31
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	1	0
Adults (18-64 years)	21	16	20
From 65-84 years	9	13	11
Age Continuous Units: years			
arithmetic mean	56	56.7	55.4
standard deviation	± 12.3	± 15.2	± 14.5
Gender, Male/Female Units: participants			
Female	22	24	16
Male	8	6	15
Asthma Attack Severity based on Asthma Prevention and Management Guideline 2003, Japan			
Mild (Peak Expiratory Flow >80%), Moderate (Peak Expiratory Flow: 60% ~ 80%), Severe (Peak Expiratory Flow <60%) or Serious (Peak Expiratory Flow: incapable measurement, cyanosis, head trip, disturbed consciousness, incontinence or asphyxia)			
Units: Subjects			
Mild	21	18	26
Moderate	9	12	5
Severe	0	0	0
Serious	0	0	0
Baseline Forced Expiratory Volume in One Second (FEV1) Units: Liters			
arithmetic mean	1.35	1.18	1.43
standard deviation	± 0.29	± 0.33	± 0.53
Duration of Asthma Units: Years			
arithmetic mean	14.9	13.9	16.7
standard deviation	± 10.4	± 11.5	± 14.1

Reporting group values	Total		

Number of subjects	91		
Age categorical Units: Subjects			
Adolescents (12-17 years)	1		
Adults (18-64 years)	57		
From 65-84 years	33		
Age Continuous Units: years arithmetic mean standard deviation	- -		
Gender, Male/Female Units: participants			
Female	62		
Male	29		
Asthma Attack Severity based on Asthma Prevention and Management Guideline 2003, Japan			
Mild (Peak Expiratory Flow >80%), Moderate (Peak Expiratory Flow: 60% ~ 80%), Severe (Peak Expiratory Flow <60%) or Serious (Peak Expiratory Flow: incapable measurement, cyanosis, head trip, disturbed consciousness, incontinence or asphyxia)			
Units: Subjects			
Mild	65		
Moderate	26		
Severe	0		
Serious	0		
Baseline Forced Expiratory Volume in One Second (FEV1) Units: Liters arithmetic mean standard deviation	- -		
Duration of Asthma Units: Years arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Montelukast 7 mg
Reporting group description: Montelukast 7 mg IV administration	
Reporting group title	Montelukast 14 mg
Reporting group description: Montelukast 14 mg IV administration	
Reporting group title	Aminophylline 250 mg
Reporting group description: Aminophylline 250 mg IV drip administration	

Primary: Change from Baseline in forced expiratory volume in one second (FEV1) within the first 60 minutes after administration

End point title	Change from Baseline in forced expiratory volume in one second (FEV1) within the first 60 minutes after administration

End point description:

The time weighted average change from Baseline in Forced Expiratory Volume in One Second (FEV1) over the first 60 minutes after study drug administration (average change FEV1 (0-60 min)). Baseline (pre-allocation) was the last measurement obtained during the screening period. Analysis was performed on data obtained from the Per Protocol Set, which is the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model.

End point type	Primary

End point timeframe:

Baseline and 60 minutes after study drug administration

End point values	Montelukast 7 mg	Montelukast 14 mg	Aminophylline 250 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27[1]	30	29[2]	
Units: Liters				
least squares mean (confidence interval 95%)	0.07 (0.02 to 0.12)	0.05 (0 to 0.11)	0.06 (0.01 to 0.12)	

Notes:

[1] - Participants receiving

[2] - 1 participant with no FEV1 data at 60 minutes was excluded from the analysis.

Statistical analyses

Statistical analysis title	Montelukast 7 mg vs. Aminophylline 250 mg

Statistical analysis description:

Treatment difference in change from Baseline in FEV1 within the first 60 minutes after study drug administration was assessed as the difference in the least square (LS) means of time weighted average change FEV1 (0-60 min) using an Analysis of Covariance (ANCOVA) model. The model included a factor for treatment and used the baseline FEV1 as a covariate.

Comparison groups	Montelukast 7 mg v Aminophylline 250 mg

Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.871
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.08

Statistical analysis title	Montelukast 14 mg vs. Aminophylline 250 mg

Statistical analysis description:

Treatment difference in change from Baseline in FEV1 within the first 60 minutes after study drug administration was assessed as the difference in the LS means of time weighted average change FEV1 (0-60 min) using an ANCOVA model. The model included a factor for treatment and used the baseline FEV1 as a covariate.

Comparison groups	Montelukast 14 mg v Aminophylline 250 mg
Number of subjects included in analysis	59
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.794
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.06

Statistical analysis title	Montelukast 7 mg vs. Montelukast 14 mg

Statistical analysis description:

Treatment difference in change from Baseline in FEV1 within the first 60 minutes after study drug administration was assessed as the difference in the LS means of time weighted average change FEV1 (0-60 min) using an ANCOVA model. The model included a factor for treatment and used the baseline FEV1 as a covariate.

Comparison groups	Montelukast 14 mg v Aminophylline 250 mg
Number of subjects included in analysis	59
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.675
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.09

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Screening through post-trial visit (up to 14 days)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.1
Reporting groups	
Reporting group title	Montelukast 7 mg
Reporting group description: Montelukast 7 mg IV administration	
Reporting group title	Montelukast 14 mg
Reporting group description: Montelukast 14 mg IV administration	
Reporting group title	Aminophylline 250 mg
Reporting group description: Aminophylline 250 mg IV drip administration	

Serious adverse events	Montelukast 7 mg	Montelukast 14 mg	Aminophylline 250 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	0 / 30 (0.00%)	1 / 31 (3.23%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
White blood cell count increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Montelukast 7 mg	Montelukast 14 mg	Aminophylline 250 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)	1 / 30 (3.33%)	3 / 31 (9.68%)
Investigations			
Glucose urine present			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
White blood cell count increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0

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