Clinical trial results:
A Phase IIa, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Worldwide, Proof-of-Concept Clinical Trial to Evaluate the Safety, Tolerability, and Efficacy of MK-8457 in Subjects with Active Rheumatoid Arthritis and an Inadequate Response or Intolerance to Anti-TNF- Therapy

Summary

EudraCT number	2012-002181-12
Trial protocol	SE GB ES DK GR IT HU AT
Global end of trial date	08 October 2013

Results information

Result version number	v1
This version publication date	16 February 2016
First version publication date	13 June 2015

Trial information

Trial identification

Sponsor protocol code	MK-8457-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01651936
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2013
Global end of trial reached?	Yes
Global end of trial date	08 October 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study assessed the safety and efficacy of MK-8457 in participants with active rheumatoid arthritis (RA) and an inadequate response or intolerance to anti-tumor necrosis factor α (anti-TNF-α) therapy. The primary hypothesis of this study was that among participants with active RA, MK-8457 100 mg twice daily (BID) was superior to placebo as measured by the change in Disease Activity Score 28 C-Reactive Protein (DAS28-CRP) after 12 weeks of treatment.

On September 12, 2013, upon the planned review of the interim data, the standing internal Data Monitoring Committee made the decision to discontinue this Phase II study because of safety reviews. The results of this study need to be interpreted with caution given the small sample size (56 participants) resulting from the early termination of the study.

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 participants. Participants in the base study were eligible for early escape at Week 12 or Week 18, only if they demonstrated a <20% improvement in both tender and swollen joint counts. If participants met the early escape criteria, participants could choose to either withdraw from the study or to continue into the safety extension portion of the study and receive MK-8457 100 mg twice daily (BID) for up to a total of 100 weeks of treatment.

Background therapy:

Participants were required to be on background methotrexate (MTX) therapy at stable doses prior to and during the base study.

Evidence for comparator: -

Actual start date of recruitment	29 August 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	76 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 3

Country: Number of subjects enrolled	Colombia: 11
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	56
EEA total number of subjects	20

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)	41
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at 53 clinical centers in the United States, Australia, Columbia, Denmark, France, Greece, Hungary, Italy, New Zealand, Poland, South Africa, Spain, and in the United Kingdom.

Pre-assignment

Screening details:

Sixty-four of 120 participants screened for the study were not randomized; 56 were excluded for not meeting at least one of the inclusion or exclusion criteria. Eight participants were being screened but were not randomized due to the early termination of the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MK-8457 100mg BID

Arm description:

MK-8457 100mg twice daily (BID) for 24 weeks

Arm type	Experimental
Investigational medicinal product name	MK-8457
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MK-8456 100mg, BID, oral daily for 24 weeks

Arm title	Placebo

Arm description:

Placebo to MK-8457 100mg twice daily (BID) for 24 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to MK-8457 100mg twice daily (BID) for 24 weeks

Number of subjects in period 1[1]	MK-8457 100mg BID	Placebo
Started	30	26
Completed	3	1
Not completed	27	25
Consent withdrawn by subject	1	1
Study Terminated By Sponsor	21	16
Adverse event, non-fatal	3	-
Transferred to other arm/group	2	8

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: Participants in the Base Study were eligible for early escape at Week 12 or Week 18 if they demonstrated a <20% improvement in both tender and swollen joint counts. Participants who met this criterion could withdraw from the base study and continued onto the Safety Extension Study (MK-8457 100 BID + MTX) for up to 76 weeks.

Period 2

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

Arms

Arm title	MK-8457 100 mg

Arm description:

MK-8457 (100mg) BID, oral, for up to 76 weeks.

Arm type	Experimental
Investigational medicinal product name	MK-8457 100mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MK-8456 100mg, BID, oral daily for up to 76 weeks

Number of subjects in period 2[2]	MK-8457 100 mg
Started	4
Completed	0
Not completed	14
Study Terminated By Sponsor	13
Lack of efficacy	1
Joined	10

Transferred in from other group/arm	10

Notes:

[2] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: Participants in the Base Study were eligible for early escape at Week 12 or Week 18 if they demonstrated a <20% improvement in both tender and swollen joint counts. Participants who met this criterion could withdraw from the base study and continued onto the Safety Extension Study (MK-8457 100 BID + MTX) for up to 76 weeks.

Four participants completed the Base Study and started the Safety Extension. Ten participants joined the Safety Extension after early escape from the Base Study.

Baseline characteristics

Reporting groups	
Reporting group title	MK-8457 100mg BID
Reporting group description:	
MK-8457 100mg twice daily (BID) for 24 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo to MK-8457 100mg twice daily (BID) for 24 weeks	

Reporting group values	MK-8457 100mg BID	Placebo	Total
Number of subjects	30	26	56
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)	21	20	41
From 65-84 years	8	6	14
85 years and over	1	0	1
Gender categorical Units: Subjects			
Female	22	21	43
Male	8	5	13

End points

End points reporting groups

Reporting group title	MK-8457 100mg BID
Reporting group description: MK-8457 100mg twice daily (BID) for 24 weeks	
Reporting group title	Placebo
Reporting group description: Placebo to MK-8457 100mg twice daily (BID) for 24 weeks	
Reporting group title	MK-8457 100 mg
Reporting group description: MK-8457 (100mg) BID, oral, for up to 76 weeks.	

Primary: Change From Baseline in the Disease Activity Score 28 C-Reactive Protein (DAS28-CRP) at Week 12

End point title	Change From Baseline in the Disease Activity Score 28 C-Reactive Protein (DAS28-CRP) at Week 12
End point description: The DAS28-CRP is a continuous parameter derived from the formula: 0.56 × the square root of the tender joint count (0-28) + 0.28 × the square root of the swelling joint count (0-28) + 0.36 × the C reactive protein value (in mg/L +1) + 0.014 × Patient's Global Assessment of Disease Activity Visual Analog Score of 0-100 mm + 0.96 = a value ranging from 2.0 to 10.0 with higher values meaning higher disease activity. A value of 2.6 was interpreted as remission.	
End point type	Primary
End point timeframe: Baseline and Week 12	

End point values	MK-8457 100mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[1]	18[2]		
Units: DAS28-CRP score				
least squares mean (confidence interval 95%)	-1.83 (-2.58 to -1.09)	-1.31 (-2.01 to -0.62)		

Notes:

[1] - Number of participants with data at both Baseline and Week 12.

[2] - Number of participants with data at both baseline and Week 12.

Statistical analyses

Statistical analysis title	Treatment Difference
Statistical analysis description: Difference in Least Squares Means between Change from Baseline in DAS-28-CRP for participants taking MK-8457 at Week 12 vs. Change from Baseline in DAS-28-CRP for participants taking placebo at Week 12. Negative differences are in favor of the MK-8457 treatment group in the comparison.	
Comparison groups	Placebo v MK-8457 100mg BID

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.308
Method	Constrained longitudinal data analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	0.5

Notes:

[3] - Constrained longitudinal data analysis model includes terms for region, screening inflammatory marker level, time in weeks, and treatment by time. A participant needs to have at least one baseline observation or post-baseline observation to be included in the model.

Secondary: Percentage of Participants Achieving American College of Rheumatology 20 (ACR20) Response at Week 12

End point title	Percentage of Participants Achieving American College of Rheumatology 20 (ACR20) Response at Week 12

End point description:

ACR responses are presented as the numerical measurement of improvement in multiple disease assessment criteria. An ACR 20 response is defined as a ≥ 20% improvement in: 1. Swollen joint count (66 joints) and tender joint count (68 joints) (0 = Absent; 1 = Present) and 2. ≥ 20% improvement in 3 of the following 5 assessments: a. A particpant's overall assessment of pain on a visual analog scale (VAS, 100 mm, no pain to extreme pain); b. Participant's Global Assessment of Disease Activity (VAS); c. Physician's Global Assessment of Disease Activity (VAS); d. Patient's assessment of function as measured by Health Assessment Questionnaire (HAQ). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area.; e. C-Reactive Protein (an inflammatory marker with a normal reference range of less than 0.9 mg/dL).

End point type	Secondary

End point timeframe:

Week 12

End point values	MK-8457 100mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[4]	26[5]		
Units: Percentage of participants				
number (not applicable)	26.67	26.92		

Notes:

[4] - Number of participants who completed Week 12 or discontinued before Week 12.

[5] - Number of participants who has either completed Week 12 or has discontinued before Week 12.

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Percentage of ACR20 responders at Week 12 treated with MK-8457 minus percentage of ACR20 responders at Week 12 treated with placebo.

Comparison groups	MK-8457 100mg BID v Placebo

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.91
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.52
upper limit	23.01

Notes:

[6] - Based on Cochran-Mantel-Haenszel test stratified by region and screening inflammatory marker level.

Secondary: Percentage of Participants Achieving an ACR20 Response at Week 24

End point title	Percentage of Participants Achieving an ACR20 Response at Week 24

End point description:

Percentage of participants who were ACR20 responders at Week 24. ACR responses were presented as the numerise assessment criteria. An ACR 20 response was defined as a ≥ 20% improvement in: 1. Swollen joint count (66 joints) and tender joint count (68 joints) (0 = Absent; 1 = Present) and 2. ≥ 20% improvement in 3 of the following 5 assessments: a. A particpant's overall assessment of pain on a visual analog scale (VAS, 100 mm, no pain to extreme pain); b. Participant's Global Assessment of Disease Activity (VAS); c. Physician's Global Assessment of Disease Activity (VAS); d. Participant's assessment of function as measured by Health Assessment Questionnaire (HAQ). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area; e. C-Reactive Protein (an inflammatory marker with a normal reference range of less than 0.9 mg/dL).

End point type	Secondary

End point timeframe:

Week 24

End point values	MK-8457 100mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[7] - Due to the early termination of the study, this endpoint was not evaluated.

[8] - Due to the early termination of the study, this endpoint was not evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR50 Response at Week 12

End point title	Percentage of Participants Achieving ACR50 Response at Week 12

End point description:

Percentage of participants who were ACR50 responders at Week 12. ACR responses are presented as

the numerical measurement of improvement in multiple disease assessment criteria. An ACR50 response is defined as a ≥ 50% improvement in: 1. Swollen joint count (66 joints) and tender joint count (68 joints) (0 = Absent; 1 = Present) and 2. ≥ 50% improvement in 3 of the following 5 assessments: a. A participant's overall assessment of pain on a visual analog scale (VAS, 100 mm, no pain to extreme pain); b. Participant's Global Assessment of Disease Activity (VAS); c. Physician's Global Assessment of Disease Activity (VAS); d. Participant's assessment of function as measured by Health Assessment Questionnaire (HAQ). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area.; e. C-Reactive Protein (an inflammatory marker with a normal reference range of less than 0.9 mg/dL).

End point type	Secondary

End point timeframe:

Week 12

End point values	MK-8457 100mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[9]	26[10]		
Units: Percentage of participants				
number (not applicable)	20	11.54		

Notes:

[9] - Number of participants who completed Week 12 or discontinued before Week 12.

[10] - Number of participants who completed Week 12 or discontinued before Week 12.

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Percentage of ACR50 responders at Week 12 treated with MK-8457 minus percentage of ACR50 responders at Week 12 treated with placebo.

Comparison groups	Placebo v MK-8457 100mg BID
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.468
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	8.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	27.32

Notes:

[11] - Based on Cochran-Mantel-Haenszel test stratified by region and screening inflammatory marker level.

Secondary: Change From Baseline in DAS28-CRP at Week 24

End point title	Change From Baseline in DAS28-CRP at Week 24

End point description:

DAS28 (CRP) is a continuous response validated measure which includes tender and swollen joint count, inflammatory marker, and patient global assessment. The DAS28 based on CRP is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), CRP, and GH. The DAS28 is a continuous parameter and is defined as follows: DAS28 (CRP) = 0.56 × SQRT(TEN28) + 0.28 × SQRT

(SW28) + 0.36 × ln (CRP+1) + 0.014 × GH + 0.96 where: TEN28 is 28 joint count for tenderness; SW28 is 28 joint count for swelling. SQRT is the square root.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	MK-8457 100mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: DAS28-CRP score				
number (not applicable)				

Notes:

[12] - Due to the early terminaton of the study, this endpoint was not evaluated.

[13] - Due to the early terminaton of the study, this endpoint was not evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Health Assessment Questionnaire (HAQ) at Week 12

End point title	Change From Baseline in the Health Assessment Questionnaire (HAQ) at Week 12

End point description:

The functional status of the participant was assessed using the Disability Index of the HAQ. This 20-question instrument assessed the degree of difficulty a person had in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	MK-8457 100mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[14]	18[15]		
Units: HAQ score				
least squares mean (confidence interval 95%)	-0.67 (-0.95 to -0.39)	-0.26 (-0.52 to -0.01)		

Notes:

[14] - Number of participants with data at both Baseline and Week 12.

[15] - Number of participants with data at both Baseline and Week 12.

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Change from baseline in HAQ at Week 12 for participants treated with MK-8457 minus change from

baseline in HAQ at Week 12 for participants treated with placebo. Negative differences are in favor of the MK-8457 treatment group in the comparison.

Comparison groups	MK-8457 100mg BID v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.038
Method	Difference in LS Means
Parameter estimate	Mean difference (final values)
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	-0.02

Notes:

[16] - Constrained longitudinal data analysis model includes terms for region, screening inflammatory marker level, time in weeks, and treatment by time. A participant needed to have at least one baseline observation or post-baseline observation to be included in the model.

Secondary: Percentage of Participants Achieving ACR50 Response at Week 24

End point title	Percentage of Participants Achieving ACR50 Response at Week 24

End point description:

Percentage of participants who were ACR50 responders at Week 24. ACR responses are presented as the numerical measurement of improvement in multiple disease assessment criteria. An ACR50 response is defined as a ≥ 50% improvement in: 1. Swollen joint count (66 joints) and tender joint count (68 joints) (0 = Absent; 1 = Present) and 2. ≥ 50% improvement in 3 of the following 5 assessments: a. A participant's overall assessment of pain on a visual analog scale (VAS, 100 mm, no pain to extreme pain); b. Participant's Global Assessment of Disease Activity (VAS); c. Physician's Global Assessment of Disease Activity (VAS); d. Participant's assessment of function as measured by Health Assessment Questionnaire (HAQ). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area; e. C-Reactive Protein (an inflammatory marker with a normal reference range of less than 0.9 mg/dL).

End point type	Secondary

End point timeframe:

Week 24

End point values	MK-8457 100mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: Percentage of Participants				
number (not applicable)				

Notes:

[17] - Due to the early termination of the study, this endpoint was not evaluated.

[18] - Due to the early termination of the study, this endpoint was not evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the HAQ at Week 24

End point title	Change From Baseline in the HAQ at Week 24

End point description:

The functional status of the participant was assessed using the Disability Index of the HAQ. This 20-question instrument assessed the degree of difficulty a person had in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	MK-8457 100mg BID	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[19]	0[20]		
Units: HAQ score				
number (not applicable)				

Notes:

[19] - Due to the early terminaton of the study, this endpoint was not evaluated.

[20] - Due to the early terminaton of the study, this endpoint was not evaluated.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 102 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	MK-8457 100 mg (Base Study)
Reporting group description: -	
Reporting group title	Placebo (Base study)
Reporting group description: -	
Reporting group title	MK-8457 100 mg (Safety Extension)
Reporting group description: -	

Serious adverse events	MK-8457 100 mg (Base Study)	Placebo (Base study)	MK-8457 100 mg (Safety Extension)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)	0 / 26 (0.00%)	2 / 14 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
White blood cell count decreased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 14 (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
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 14 (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
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 14 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 26 (0.00%)	0 / 14 (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
Lung infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 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	MK-8457 100 mg (Base Study)	Placebo (Base study)	MK-8457 100 mg (Safety Extension)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 30 (33.33%)	2 / 26 (7.69%)	6 / 14 (42.86%)
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Mouth injury			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 26 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 26 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	2 / 30 (6.67%)	0 / 26 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	5 / 30 (16.67%)	1 / 26 (3.85%)	2 / 14 (14.29%)
occurrences (all)	5	1	3
Dyspepsia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 26 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2013	This amendment was a global amendment and included changes to the primary and secondary objectives, reduction in the sample size, and removal of the second planned interim analysis. No participants were enrolled under this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 September 2013	On September 12, 2013, upon the planned review of the interim data, the standing internal Data Monitoring Committee made the decision to discontinue this Phase II study because of safety reviews.	-

Notes:

Limitations and caveats

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

The results of this study need to be interpreted with caution given the small sample size (56 participants) resulting from the early termination of the study.

Notes: