Clinical trial results:
A Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Worldwide, Dose-Ranging Clinical Trial with a Proof-of-Concept Lead Cohort to Evaluate the Safety, Tolerability, and Efficacy of MK-8457 + MTX in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy

Summary

EudraCT number	2012-000439-17
Trial protocol	LT DE GB DK PL HU LV
Global end of trial date	22 October 2013

Results information

Result version number	v1
This version publication date	01 April 2016
First version publication date	24 June 2015

Trial information

Trial identification

Sponsor protocol code	8457-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01569152
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol number: P08683, Merck Registration: MK-8457-008

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trial 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	22 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 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 + methotrexate (MTX) in participants with active rheumatoid arthritis (RA) despite MTX therapy. The primary hypothesis was that at least 1 dose of MK-8457 + MTX was superior to placebo + MTX as measured by the proportion of participants who achieved American College of Rheumatology 20 (ACR 20) response 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 (82 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 all treatment groups in the base study were eligible for early escape at any point after Week 12 if they demonstrated a < 20% improvement in both tender and swollen joint counts. Participants could withdraw from the study or early escape and receive MK-8457 100mg twice daily (BID) in the safety extension portion of the study.

Background therapy:

Participants were treated with methotrexate (MTX) for at least 3 months immediately prior to screening and continued on a stable weekly dose during the study.

Evidence for comparator: -

Actual start date of recruitment	22 May 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: 4
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Canada: 1

Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Moldova, Republic of: 19
Worldwide total number of subjects	82
EEA total number of subjects	19

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)	66
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at 58 trial centers in the United States, Canada, Chile, Denmark, South Africa, Germany, Hungary, Japan, Lithuania, Moldova, Poland, South Korea, Taiwan, and in the United Kingdom.

Pre-assignment

Screening details:

One hundred and thirty-one of 213 participants screened for study were not randomized; 124 participants were excluded for not meeting at least one of the inclusion or exclusion criteria. Six participants withdrew from the study and 1 participant was 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-8457 100mg BID for 24 weeks

Arm title	Placebo

Arm description:

Placebo to MK-8457 100mg 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 BID for 24 weeks

Number of subjects in period 1	MK-8457 (100mg BID)	Placebo
Started	41	41
Completed	20	9
Not completed	21	32
Consent withdrawn by subject	2	1
Study terminated by Sponsor	9	8
Adverse event, non-fatal	4	-
Early Escape into Extension	5	22
Non-compliance with study drug	-	1
Lost to follow-up	1	-

Period 2

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

Arms

Arm title	MK-8457

Arm description:

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

Number of subjects in period 2[1]	MK-8457
Started	29
Completed	0
Not completed	55
Physician decision	2
Consent withdrawn by subject	2
Study terminated by Sponsor	47

Adverse event, non-fatal	4
Joined	26
Transferred in from other group/arm	26

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 from the base study and continue onto the Safety Extension Study after Week 12 if they demonstrated a < 20% improvement in both tender and swollen joint counts.

Twenty-nine participants completed the Base Study and started the Safety Extension. Twenty-six participants joined the Safety Extension after early escape from the Base Study because 1 participant (Placebo Group) who was an early escape did not join the Safety Extension.

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 BID for 24 weeks	

Reporting group values	MK-8457 (100mg BID)	Placebo	Total
Number of subjects	41	41	82
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)	35	31	66
From 65-84 years	6	10	16
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	30	33	63
Male	11	8	19

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 BID for 24 weeks	
Reporting group title	MK-8457
Reporting group description: MK-8457 (100mg BID) for up to 76 weeks	

Primary: Percentage of Participants Achieving an American College of Rheumatology (ACR) 20 Response at Week 12

End point title	Percentage of Participants Achieving an American College of Rheumatology (ACR) 20 Response at Week 12
End point description: ACR responses are numerical measurements 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 participant's overall assessment of pain on a visual analog scale (VAS, 100 mm, no pain to extreme pain; b. Patient's Global Assessment of Disease Activity (VAS) participant doing very well (0) to very poor (100); 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	Primary
End point timeframe: Week 12	

End point values	MK-8457 (100mg BID)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[1]	41[2]		
Units: Percentage of subjects				
number (not applicable)	68.29	24.39		

Notes:

[1] - Number of participants who have either completed Week 12 or have discontinued before Week 12.

[2] - Number of participants who have either completed Week 12 or have 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	Placebo v MK-8457 (100mg BID)

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference of percentages
Point estimate	43.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.52
upper limit	63.28

Notes:

[3] - The primary efficacy analysis was based on the Full Analysis Set (FAS) population using the Cochran-Mantel-Haenszel (CMH) method stratified by CRP strata. A last observation carried forward procedure was used to impute the missing ACR20 components if the participants had data for at least 1 component at Week 12. If participants did not have data for any of the ACR components at Week 12, the participant was considered not to have achieved an ACR20 response.

Secondary: Change from Baseline in Disease Activity Score (DAS-28) as Measured by Erythrocyte Sedimentation Rate (ESR) At Week 12

End point title	Change from Baseline in Disease Activity Score (DAS-28) as Measured by Erythrocyte Sedimentation Rate (ESR) At Week 12

End point description:

The DAS28 based on ESR is a continuous parameter based upon a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), (ESR, an inflammatory marker), and Patient's Global Assessment of Disease Activity (GH, on a visual analog scale (VAS) of 100 mm). It is a continuous parameter and is defined as follows: DAS 28 (ESR) = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.70 × ln (ESR) + 0.014 × GH. SQRT = square root. TEN28 is 28 joint count for tenderness and SW28 is 28 joint count for swelling. The DAS28 is a scale ranging from 0 to 10 indicating current RA disease activity. Depending upon the DAS28 value, improvement from baseline is No Response (>= 0.6), No response to Moderate Response (>0.6 - 1.2), and Moderate to Good Reponse (>1.2).

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	37[4]	39[5]		
Units: DAS-28				
least squares mean (confidence interval 95%)	-2 (-2.4 to -1.61)	-1.02 (-1.41 to -0.64)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Difference in the least squares means between change from baseline in DAS28-ESR for participants taking MK-8457 at Week 12 vs. change from baseline in DAS28-ESR for participants taking placebo at

Week 12. 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	76
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	-0.43

Notes:

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

Secondary: Change from Baseline in DAS28 as Measured by C-Reactive Protein (CRP) at Week 12

End point title	Change from Baseline in DAS28 as Measured by C-Reactive Protein (CRP) at Week 12

End point description:

The DAS28 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	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	37[7]	39[8]		
Units: DAS28-CRP				
least squares mean (confidence interval 95%)	-1.98 (-2.34 to -1.61)	-0.87 (-1.23 to -0.51)		

Notes:

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

[8] - 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	MK-8457 (100mg BID) v Placebo

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Difference of percentages
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	-0.6

Notes:

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

Secondary: Percentage of Participants Achieving an ACR70 Response at Week 12

End point title	Percentage of Participants Achieving an ACR70 Response at Week 12

End point description:

ACR responses are presented as the numerical measurement of improvement in multiple disease assessment criteria. An ACR 70 response is defined as a ≥ 70% improvement in: 1. Swollen joint count (66 joints) and tender joint count (68 joints) (0 = Absent; 1 = Present) and 2. ≥ 70% 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. Patient'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	41[10]	41[11]		
Units: Percentage of Subjects				
number (not applicable)	19.51	4.88		

Notes:

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

[11] - Number of participants who have either completed Week 12 or have discontinued before Week 12.

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Percentage of participants treated with MK-8457 that were an ACR70 responder at Week 12 minus percentage of participants treated with placebo that were an ACR70 responder at Week 12.

Comparison groups	MK-8457 (100mg BID) v Placebo

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.044
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentages
Point estimate	14.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	28.44

Notes:

[12] - Cochran-Mantel-Haenszel test stratified by screening CRP level.

Secondary: Percentage of Participants Achieving Hybrid ACR Response at Week 12

End point title	Percentage of Participants Achieving Hybrid ACR Response at Week 12

End point description:

Hybrid ACR Response evaluates the improvement in active RA by combining elements of the ACR20/50/70 with a continuous score of the mean change in each of the core set measures. The percentage improvement from baseline was computed in each of the 7 core components of the ACR. The average percent improvement was calculated and used with the participant's ACR20, ACR50, and ACR70 status to compute the hybrid ACR response, with a positive change indicating improvement.

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	0[13]	0[14]		
Units: Percentage of Subjects				
number (not applicable)				

Notes:

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

[14] - 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 an ACR-N Response at Week 12

End point title	Percentage of Participants Achieving an ACR-N Response at Week 12

End point description:

The ACR-N Index of Improvement is defined as the minimum of the following 3 criteria:
1. The percent improvement from baseline in tender joint counts
2. The percent improvement from baseline in swollen joint counts

3. The median percent improvement from baseline for the following 5 assessments:
    a. Participant's assessment of pain (VAS)
    b. Participant's global assessment of disease activity (VAS)
    c. Physician's global assessment of disease activity (VAS)
    d. Participant's assessment of physical function as measured by the HAQ
    e. CRP levels

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	0[15]	0[16]		
Units: Percentage of participants				
number (not applicable)				

Notes:

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

[16] - 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 a DAS-28 ESR Response at Week 12

End point title	Percentage of Participants Achieving a DAS-28 ESR Response at Week 12

End point description:

The DAS28 based on ESR is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), Erythrocyte Sedimentation Rate (ESR), and Patient's Global Assessment of Disease Activity (GH, on a VAS of 100 mm). It is a continuous parameter and is defined as follows: DAS 28 (ESR) = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.70 × ln (ESR) + 0.014 × GH. SQRT = square root. TEN28 is 28 joint count for tenderness and SW28 is 28 joint count for swelling. Depending upon the DAS28 value, improvement from baseline is No Response (>= 0.6), No response to Moderate Response (>0.6 - 1.2), and Moderate to Good Reponse (>1.2). DAS28 response was defined as "Good" or "Moderate" response categories at a visit.

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	41[17]	41[18]		
Units: Percentage of Subjects				
number (not applicable)	70.73	39.02		

Notes:

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

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

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Percentage of participants taking MK-8457 who achieved a DAS28-ESR response on Week 12 minus the percentage of participants taking placebo who achieved a DAS28-ESR response on Week 12.

Comparison groups	MK-8457 (100mg BID) v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentages
Point estimate	31.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.29
upper limit	52.13

Notes:

[19] - Based on Cochran-Mantel-Haenszel test stratified by screening ESR level.

Secondary: Percentage of Participants Achieving a DAS-28 CRP Response at Week 12

End point title	Percentage of Participants Achieving a DAS-28 CRP Response 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	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	41[20]	41[21]		
Units: Percentage of subjects				
number (not applicable)	73.17	43.9		

Notes:

[20] - Number of participants who have either completed Week 12 or have discontinued before Week 12.

[21] - Number of participants who have either completed Week 12 or have discontinued before Week 12.

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Percentage of subjects treated with MK-8457 who achieved a DAS28-CRP response score at Week 12 minus percentage of subjects treated with placebo who achieved a DAS28-CRP response score at Week 12.

Comparison groups	MK-8457 (100mg BID) v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentages
Point estimate	29.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.9
upper limit	49.63

Notes:

[22] - Constrained longitudinal data analysis model includes terms for region, screening inflammatory marker level, time in weeks, and treatment by time.

Secondary: Percentage of Participants Achieving DAS28-ESR Remission at Week 12

End point title	Percentage of Participants Achieving DAS28-ESR Remission at Week 12

End point description:

The DAS28 based on ESR is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), Erythrocyte Sedimentation Rate (ESR), and Patient's Global Assessment of Disease Activity (GH, on a VAS of 100 mm). It is a continuous parameter and is defined as follows: DAS 28 (ESR) = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.70 × ln (ESR) + 0.014 × GH. SQRT = square root. TEN28 is 28 joint count for tenderness and SW28 is 28 joint count for swelling. Depending upon the DAS28 value, improvement from baseline is No Response (>= 0.6), No response to Moderate Response (>0.6 - 1.2), and Moderate to Good Response (>1.2). DAS28 remission was defined as a DAS28 value of < 2.6 at a visit.

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	41[23]	41[24]		
Units: Percentage of participants				
number (not applicable)	9.76	0		

Notes:

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

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

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Percentage of participants treated with MK-8457 who have achieved DAS28-ESR remission at Week 12 minus percentage of participants treated with placebo who have achieved DAS28-ESR remission at

Week 12.

Comparison groups	MK-8457 (100mg BID) v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.039
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentages
Point estimate	9.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	18.84

Notes:

[25] - Based on Cochran-Mantel-Haenszel test stratified by screening CRP level.

Secondary: Percentage of Participants Achieving DAS-28 CRP Remission at Week 12

End point title	Percentage of Participants Achieving DAS-28 CRP Remission at Week 12

End point description:

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. DAS28 remission is defined as a DAS28 value of < 2.6 at a visit.

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	41[26]	41[27]		
Units: Percentage of participants				
number (not applicable)	12.2	0		

Notes:

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

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

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

Percentage of participants treated with MK-8457 who have achieved DAS28-CRP remission at Week 12 minus percentage of participants treated with placebo who have achieved DAS28-CRP remission at Week 12.

Comparison groups	MK-8457 (100mg BID) v Placebo

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentages
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.18
upper limit	22.21

Notes:

[28] - Based on Cochran-Mantel-Haenszel test stratified by screening CRP level.

Secondary: DAS-28 Area Under the Curve (AUC)

End point title	DAS-28 Area Under the Curve (AUC)

End point description:

DAS28 area under the disease activity curve (AUC) was calculated from the DAS28 score versus time curve, which provided an assessment of changes in disease activity over time. AUC DAS28 was averaged over study days. The DAS28 AUC was calculated using the trapezoidal rule as the DAS28 multiplied by the duration of the assessment period (in weeks) and was presented as %-weeks. Higher calculated AUC values indicate higher disease activity (worse).

End point type	Secondary

End point timeframe:

Up to 12 Weeks

End point values	MK-8457 (100mg BID)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[29]	0[30]		
Units: DAS-28 AUC				
number (not applicable)				

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tender Joint Count at Week 12

End point title	Change from Baseline in Tender Joint Count at Week 12

End point description:

Tender Joint Count was examined on 68 joints of the fingers, elbows, hips, knees, ankles, and toes distal for pain in response to pressure or passive motion at the study time points. Joint pain was scored as 0 = Absent; 1 = Present for each joint. Change from baseline in tender joint count was calculated as Tender Joint Count at Week 12 minus Tender Joint Count at Baseline. The overall Tender Joint Count count ranged from 0 to 68. A higher score indicated greater disease severity.

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	38[31]	39[32]		
Units: Tender Joint Count				
least squares mean (confidence interval 95%)	-13.53 (-16.73 to -10.34)	-8.78 (-11.96 to -5.6)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Difference in the Least Squares Mean

Statistical analysis description:

Change from baseline in the least squares mean of tender joint count at Week 12 for participants treated with MK-8457 minus change from baseline in the least squares mean of Tender Joint Count at Week 12 for participants treated with placebo. 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	77
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.028
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.99
upper limit	-0.52

Notes:

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

Secondary: Change from Baseline in Swollen Joint Count at Week 12

End point title	Change from Baseline in Swollen Joint Count at Week 12

End point description:

Swollen joint count included 66 joints (same joints as for tender joint count except this excluded evaluation of hips) that were assessed for the presence of swelling. Soft tissue swelling was considered to be present if there was palpable or visible evidence of capsular distention considered to be due to either synovial thickening and/or a joint effusion. Bony swelling, nodule formation, and joint deformity were excluded from consideration. A swollen joint was scored as 0 = Absent; 1 = Present for each joint. The overall swollen joint count ranged from 0 to 66. A higher score indicated greater disease severity.

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	38[34]	39[35]		
Units: Swollen Joint Count				
least squares mean (confidence interval 95%)	-10.29 (-13.01 to -7.58)	-7.65 (-10.34 to -4.95)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean

Statistical analysis description:

Change from baseline in least squares mean at Week 12 for participants treated with MK-8457 minus change from baseline in least squares mean for participants 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	77
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.11
Method	Constrained Longitudinal Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.91
upper limit	0.62

Notes:

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

Secondary: Change from Baseline in Simplified Disease Activity Index (SDAI) at Week 12

End point title	Change from Baseline in Simplified Disease Activity Index (SDAI) at Week 12

End point description:

SDAI is the simple linear sum of the outcome parameters: tender joint count (TJC) and swollen joint count (SJC) based on a 28-joint assessment, patient global assessment of disease activity [PGA visual analogue scale (VAS) 0 to 10cm], physician global assessment of disease activity (MDGA VAS 0–10cm) and C-reactive protein levels (CRP in mg/dL). SDAI =TJC + SJC + PGA + MDGA + CRP. Overall scores can range from 0.1 to 86.0. A higher score indicated greater disease severity.

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	37[37]	39[38]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-23.73 (-28.5 to -18.96)	-13.17 (-17.9 to -8.45)		

Notes:

[37] - Number of Participants with data at both Baseline and Week 12.

[38] - Number of Participants with data at both Baseline and Week 12.

Statistical analyses

Statistical analysis title	Difference in Least Squares Means

Statistical analysis description:

Change from baseline in least squares means of SDAI at Week 12 for participants treated with MK-8457 minus change from baseline in least squares means of SDAI 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	76
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.002
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-10.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.97
upper limit	-4.15

Notes:

[39] - Constrained longitudinal data analysis model includes terms for region, screening inflammatory marker level, time in weeks, and treatment by time. A participant had to have at least one baseline observation or post-baseline observation to be included in the model. Negative differences are in favor of the MK-8457 treatment group in the comparison.

Secondary: Change from Baseline in Short Form Health Survey (SF-36) at Week 12

End point title	Change from Baseline in Short Form Health Survey (SF-36) at Week 12

End point description:

The SF-36 is a health-related quality of life instrument that consists of 8 multi-item scales: limitations in physical functioning due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities due to personal or emotional problems, limitations in social functioning due to physical or mental health problems, vitality (energy and fatigue), and general health perception. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing the comparison of relative burden of disease and relative benefit of different treatments. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score the greater the disability i.e., a score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability.

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	0[40]	0[41]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

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

[41] - 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 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at Week 12

End point title	Change from Baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) at Week 12

End point description:

The Functional Assessment of Chronic Illness Therapy (FACIT-F) is a questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. FACIT-F is a 13-item questionnaire. Participants scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). The larger the participant's response to the questions, the greater the participants fatigue.

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	0[42]	0[43]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

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

[43] - 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 Patient's Global Assessment of Disease

Status/Activity (GADSA) at Week 12

End point title	Change from Baseline in the Patient's Global Assessment of Disease Status/Activity (GADSA) at Week 12

End point description:

Patient's Global Assessment of Disease Status/Activity (PGDSA) are measured using a visual analog scale with scores ranging from 0 to 100mm (VAS; 0mm [best] to 100mm [worst]) with increasing scores indicating increased level of disease. A negative value in change from baseline indicates an improvement.

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	37[44]	39[45]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-29.06 (-35.93 to -22.19)	-8.21 (-15 to -1.43)		

Notes:

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

[45] - 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 Patient Global Assessment of Disease Activity at Week 12 for participants treated with MK-8457 minus change from baseline in Patient Global Assessment of Disease Activity 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	76
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-20.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.98
upper limit	-11.71

Notes:

[46] - Constrained longitudinal data analysis model includes terms for region, screening inflammatory marker level, time in weeks, and treatment by time. A participant had to have at least one baseline observation or post-baseline observation to be included in the model. Negative differences are in favor of the MK-8457 treatment group in the comparison.

Secondary: Change from Baseline in the Patient's Global Assessment of Pain (PGAP) at Week 12

End point title	Change from Baseline in the Patient's Global Assessment of Pain (PGAP) at Week 12

End point description:

A participant's overall assessment of pain was assessed from the amount of pain due to arthritis experienced during the past 48 hours on a visual analog scale (VAS, 100mm VAS scale—0mm "no pain," 100mm "extreme pain.").

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	37[47]	39[48]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-28.85 (-37.17 to -20.54)	-8.17 (-16.42 to 0.09)		

Notes:

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

[48] - 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 Patient Global Assessment of Pain at Week 12 for participants treated with MK-8457 minus change from baseline in Patient Global Assessment of Pain at Week 12 for participants treated with placebo.

Comparison groups	MK-8457 (100mg BID) v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-20.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.29
upper limit	-10.09

Notes:

[49] - Constrained longitudinal data analysis model includes terms for region, screening inflammatory marker level, time in weeks, and treatment by time. A participant had to have at least one baseline observation or post-baseline observation to be included in the model. Negative differences are in favor of the MK-8457 treatment group in the comparison.

Secondary: Change from Baseline in the Health Assessment Questionnaire Disability (HAQ) Subscales at Week 12

End point title	Change from Baseline in the Health Assessment Questionnaire Disability (HAQ) Subscales 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 assesses the degree of difficulty a person has 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. The overall score for the Disability Index is the mean of the 8 functional area scores and also ranges from 0 to 3, with a lower score indicating less disability.

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	38[50]	39[51]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-0.67 (-0.83 to -0.51)	-0.05 (-0.21 to 0.11)		

Notes:

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

[51] - 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	77
Analysis specification	Pre-specified
Analysis type	other[52]
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	-0.4

Notes:

[52] - Constrained longitudinal data analysis model includes terms for region, screening inflammatory marker level, time in weeks, and treatment by time. A participant had to have at least one baseline observation or post-baseline observation to be included in the model. Negative differences are in favor of the MK-8457 treatment group in the comparison.

Secondary: Change from Baseline in Serum CRP at Week 12

End point title	Change from Baseline in Serum CRP at Week 12

End point description:

C-Reactive Protein is an inflammatory marker with a normal reference range of less than 0.9 mg/dL.

Change from Baseline in CRP at Week 12 (Week 12 score minus Baseline score).

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	38[53]	39[54]		
Units: mg/dL				
least squares mean (confidence interval 95%)	-0.76 (-1.66 to 0.14)	0.83 (-0.07 to 1.73)		

Notes:

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

[54] - 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 CRP at Week 12 for participants treated with MK-8457 minus change from baseline in CRP 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	77
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.007
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	-0.45

Notes:

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

Secondary: Change from Baseline in ESR at Week 12

End point title	Change from Baseline in ESR at Week 12

End point description:

The ESR is the rate at which red blood cells sediment in a period of one hour, and is a non-specific measure of inflammation. Change from Baseline in ESR equals score at Week 12 minus score at Baseline.

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	38[56]	39[57]		
Units: mm/h				
least squares mean (confidence interval 95%)	-6.8 (-13.98 to 0.38)	-1.9 (-9.03 to 5.23)		

Notes:

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

[57] - 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 ESR at Week 12 (score for participants treated with MK-8457 minus score for participants treated with placebo). Number of participants with data at both baseline and Week 12. 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	77
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.315
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.54
upper limit	4.74

Notes:

[58] - 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: Change from Baseline in Hemoglobin at Week 12

End point title	Change from Baseline in Hemoglobin at Week 12

End point description:

Change from Baseline in hemoglobin equals Week 12 values minus baseline values for participants treated with MK-8457 or placebo. Hemoglobin is the iron-containing oxygen-transport metalloprotein in red blood cells.

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	39[59]	39[60]		
Units: gm/dL				
arithmetic mean (standard deviation)	0.11 (± 0.83)	-0.07 (± 0.86)		

Notes:

[59] - The number of participants in each treatment group with non-missing Baseline and Week 12 values.
[60] - The number of participants in each treatment group with non-missing Baseline and Week 12 values.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an ACR50 Response at Week 12

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

End point description:

Percentage of participants who were ACR50 responders at Week 12 with ACR responses presented as the numerical measurement of improvement in multiple disease assessment criteria. An ACR 50 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. Patient'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:

Baseline and Week 12

End point values	MK-8457 (100mg BID)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[61]	41[62]		
Units: Percentage of participants				
number (not applicable)	36.59	4.88		

Notes:

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

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

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

ACR50 response rate at Week 12 for participants treated with MK-8457 minus ACR50 response rate at Week 12 for participants treated with placebo.

Comparison groups	MK-8457 (100mg BID) v Placebo

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	31.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.56
upper limit	47.86

Notes:

[63] - Based on Cochran-Mantel-Haenszel test stratified by screening CRP level.

Secondary: ACR20 Response Rate Over Time

End point title	ACR20 Response Rate Over Time

End point description:

Percentage of participants who were ACR20 responders at Week 1, 2, 4, 6, 12, 18, and 24 with ACR responses 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 participant's overall assessment of pain on a visual analog scale (VAS, 100 mm, no pain to extreme pain); b. Patient'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, no difficulty, to 3, 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:

Baseline, Week 1, Week 2, Week 4, Week 6, Week 12, Week 18, Week 24

End point values	MK-8457 (100mg BID)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[64]	41[65]		
Units: Percentage of Participants				
number (not applicable)				
Week 1	12.2	9.8		
Week 2	51.2	14.6		
Week 4	61	22		
Week 6	63.4	14.6		
Week 12	68.3	24.4		
Week 18	53.7	12.2		
Week 24	48.8	22		

Notes:

[64] - The number of participants in each treatment group at particular weeks.

[65] - The number of participants in each treatment group at particular weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Investigator's Global Assessment of Disease Status/Activity (IGADSA) at Week 12

End point title	Change from Baseline in the Investigator's Global Assessment of Disease Status/Activity (IGADSA) at Week 12

End point description:

Investigator's Global Assessment of Disease Status/Activity (IGADSA) is measured using a visual analog scale with scores ranging from 0 to 100mm (VAS; 0mm [best] to 100mm [worst]) with increasing scores indicating how well the participant was doing. A negative value in change from baseline indicates an improvement.

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	38[66]	39[67]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-34.21 (-41.8 to -26.63)	-14.73 (-22.23 to -7.23)		

Notes:

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

[67] - 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 IGADA at Week 12 for participants treated with MK-8457 minus change from baseline in IGADA 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	77
Analysis specification	Pre-specified
Analysis type	other[68]
P-value	< 0.001
Method	Constrained Longitudinal Data Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-19.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.69
upper limit	-9.28

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 104 weeks

Adverse event reporting additional description:

Adverse events were reported for participants treated with MK-8457 100 mg for up to 76 weeks in the Safety Extension.

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:

Participants who received at least one dose of MK-8457 100 mg during the Base Study.

Reporting group title	Placebo (Base Study)

Reporting group description:

Participants who received at least one dose of placebo to MK-8457 during the Base Study.

Reporting group title	MK-8457 100 mg (Safety Extension)

Reporting group description:

Participants who received at least one dose of MK-8457 100 mg during the Safety Extension.

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	2 / 41 (4.88%)	0 / 41 (0.00%)	3 / 55 (5.45%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 55 (3.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumonia pneumococcal			

subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 55 (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
Pneumonia viral			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 55 (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

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	15 / 41 (36.59%)	9 / 41 (21.95%)	11 / 55 (20.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 41 (4.88%)	1 / 41 (2.44%)	3 / 55 (5.45%)
occurrences (all)	2	1	5
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	3 / 55 (5.45%)
occurrences (all)	1	0	4
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	1 / 55 (1.82%)
occurrences (all)	3	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	1 / 55 (1.82%)
occurrences (all)	3	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 41 (9.76%)	0 / 41 (0.00%)	1 / 55 (1.82%)
occurrences (all)	4	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 41 (2.44%)	3 / 41 (7.32%)	0 / 55 (0.00%)
occurrences (all)	1	3	0
Nausea			

subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	1 / 55 (1.82%)
occurrences (all)	3	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 41 (2.44%)	3 / 41 (7.32%)	3 / 55 (5.45%)
occurrences (all)	1	3	3
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	5 / 41 (12.20%)	1 / 41 (2.44%)	2 / 55 (3.64%)
occurrences (all)	5	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2012	Additional blood pressure assessment time points were added to the study; in order to better characterize the effects of MK-8457 on blood pressure in participants with rheumatoid arthritis. Pharmacokinetic sampling time points shifted to coincide with additional blood pressure monitoring timepoints for simplicity.
08 August 2013	The doses of study drug was changed to 100mg BID, 150mg QD, 75mg QD, 25mg QD, and placebo. The time point for the primary endpoint was changed to 12 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 September 2013	On September 12, 2013, prior to the initiation of the dose-ranging portion of the trial, the Data Monitoring Committee made the decision to discontinue this Phase II study (PN008) with MK-8457 for the treatment of rheumatoid arthritis 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 (82 participants) resulting from the early termination of the study.

Notes: