Clinical trial results:
A Phase 4 Trial Assessing the ImPact of Residual Inflammation Detected Via Imaging TEchniques, Drug Levels and Patient Characteristics on the Outcome of Dose TaperIng of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) Subjects (PREDICTRA)

Summary

EudraCT number	2014-001114-26
Trial protocol	DE IE GB SE ES HU IT NL AT GR FR
Global end of trial date	08 August 2018

Results information

Result version number	v1 (current)
This version publication date	11 August 2019
First version publication date	11 August 2019

Trial information

Trial identification

Sponsor protocol code	M14-500

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02198651
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110,
Scientific contact	Ivan Lagunes, AbbVie, ivan.lagunesgalindo@abbvie.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 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to investigate the association between residual disease activity at Baseline as detected by Magnetic Resonance Imaging (MRI) and the occurrence of flares in subjects with rheumatoid arthritis (RA) randomized to an adalimumab dose tapering regimen controlled by adalimumab withdrawal. The study included a Screening period of up to 28 days (unless extended with approval of study-designated physician), a 4-week Lead-In Period with open label (OL) 40 mg adalimumab administered subcutaneously (sc) every other week (eow), and a randomized 36-week double-blind period with 40 mg adalimumab sc every 3 weeks (q3wks; tapering arm) or placebo sc q3wks (withdrawal arm). Subjects were randomized in a 5:1 ratio (tapering arm: withdrawal arm) after confirmation of meeting the disease activity score (DAS) criteria. Subjects who experienced a protocol-defined flare at any time were to enter a rescue arm with OL 40 mg adalimumab administered sc eow for 16 weeks.

Protection of trial subjects:

Prior to the initiation of any screening or study-specific procedures, the investigator or his or her representative explained the nature of the study to the subject or his or her representative and answered all questions regarding this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	United Kingdom: 12

Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	149
EEA total number of subjects	113

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)	93
From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

146 subjects enrolled in the study and received at least 1 dose of study drug during the Lead-in period. Three subjects enrolled in the study but were not treated during the Lead-in period.

Period 1

Period 1 title	Lead-in Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Adalimumab 40 mg Eow

Arm description:

40 mg adalimumab administered subcutaneously every other week (eow) from Week 0 to Week 4 (Lead-in Period)

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg adalimumab administered subcutaneously every other week (eow) from Week 0 to Week 4 (Lead-in Period)

Number of subjects in period 1[1]	Adalimumab 40 mg Eow
Started	146
Subjects treated in Lead-in Period	146
Completed	110
Not completed	36
Consent withdrawn by subject	12
Adverse event, non-fatal	2
Other, not specified	22

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The All Lead-in-Treated Subject population consists of subjects who were enrolled in the study and received at least 1 dose of study drug during the Lead-in period. Three participants enrolled in the study but were not treated during the Lead-in period.

Period 2

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

Arms

Are arms mutually exclusive?	No
Arm title	Adalimumab Tapering

Arm description:

40 mg adalimumab administered subcutaneously every three weeks from Week 4 to Week 40 (Double-blind Period)

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg adalimumab administered subcutaneously every three weeks from Week 4 to Week 40 (Double-blind Period)

Arm title	Adalimumab Withdrawal Arm

Arm description:

Placebo administered subcutaneously every three weeks from Week 4 to Week 40 (Double-blind Period)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo administered subcutaneously every three weeks from Week 4 to Week 40 (Double-blind Period)

Number of subjects in period 2	Adalimumab Tapering	Adalimumab Withdrawal Arm
Started	102	20
Completed	93	19
Not completed	9	1
Consent withdrawn by subject	4	-
Adverse event, non-fatal	1	-
Other, not specified	4	1

Period 3

Period 3 title	Open-Label Rescue Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab Tapering to Rescue Arm

Arm description:

40 mg adalimumab administered subcutaneously every other week (eow) from Flare Week 0 to Flare Week 16 (Open-Label Rescue Period)

Arm type	Experimental
Investigational medicinal product name	Adalimumab 40 mg eow Rescue Arm
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg adalimumab administered subcutaneously every other week from Flare Week 0 to Flare Week 16 (Open-label Rescue Period)

Arm title	Adalimumab Withdrawal to Rescue Arm

Arm description:

40 mg adalimumab administered subcutaneously every other week (eow) from Flare Week 0 to Flare Week 16 (Open-Label Rescue Period)

Arm type	Experimental
Investigational medicinal product name	Adalimumab 40 mg eow Rescue Arm
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg adalimumab administered subcutaneously every other week from Flare Week 0 to Flare Week 16 (Open-label Rescue Period)

Number of subjects in period 3	Adalimumab Tapering to Rescue Arm	Adalimumab Withdrawal to Rescue Arm
Started	31	8
Completed	28	8
Not completed	3	0
Consent withdrawn by subject	2	-
Incorrectly entered Open-Label Rescue Period	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Lead-in Period
Reporting group description:	
All Lead-in-Treated Subject population: participants who were enrolled in the study and received at least 1 dose of study drug during the Lead-in period. Three participants enrolled in the study but were not treated during the Lead-in period.	

Reporting group values	Lead-in Period	Total	
Number of subjects	146	146	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 59.6 ± 10.30	 -	
Gender categorical Units: Subjects			
Female	109	109	
Male	37	37	
Tobacco Use Units: Subjects			
Current	22	22	
Former	46	46	
Never	76	76	
Unknown	2	2	
Previous treatment with conventional synthetic disease modifying antirheumatic drugs (csDMARDs) Units: Subjects			
Yes	145	145	
No	1	1	
Previous Tx with biological disease-modifying anti-rheumatic drugs (bDMARDs; excluding adalimumab) Units: Subjects			
Yes	38	38	
No	108	108	
Previous Tx with csDMARDS or bDMARDs (excluding adalimumab) Units: Subjects			
Yes	146	146	
No	0	0	
Disease duration			
Participants with available data, n=142			
Units: years arithmetic mean standard deviation	 12.9 ± 9.99	 -	

Duration of adalimumab therapy Units: years arithmetic mean standard deviation	 5.4 ± 3.27	 -	
Duration of remission			
Participants with available data, n=125			
Units: years arithmetic mean standard deviation	 2.2 ± 1.99	 -	
Participants' Global Assessment of Disease Activity			
Participants rated the severity of their rheumatoid arthritis symptoms and how well they were doing during the last 24 hours by placing a vertical mark on a line with a range of 0 (very well) to 100 mm (very poorly).			
Units: units on a scale arithmetic mean standard deviation	 8.7 ± 11.84	 -	
Mean C-Reactive Protein (CRP)			
C-Reactive Protein (CRP; mg/L) was measured from blood samples as a marker for inflammation.			
Units: mg/L arithmetic mean standard deviation	 2.4 ± 2.58	 -	
HAQ-DI Score			
The Health Assessment Questionnaire- Disability Index (HAQ-DI) is specific for rheumatoid arthritis. 20 questions refer to eight domains:dressing/grooming, arising, eating, walking, hygiene, reach, grip, and daily activities. Participants rated their ability to do each task over the past 7 days: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task were summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability.			
Units: units on a scale arithmetic mean standard deviation	 0.4 ± 0.51	 -	

End points

End points reporting groups

Reporting group title	Adalimumab 40 mg Eow

Reporting group description:

40 mg adalimumab administered subcutaneously every other week (eow) from Week 0 to Week 4 (Lead-in Period)

Reporting group title	Adalimumab Tapering

Reporting group description:

40 mg adalimumab administered subcutaneously every three weeks from Week 4 to Week 40 (Double-blind Period)

Reporting group title	Adalimumab Withdrawal Arm

Reporting group description:

Placebo administered subcutaneously every three weeks from Week 4 to Week 40 (Double-blind Period)

Reporting group title	Adalimumab Tapering to Rescue Arm

Reporting group description:

40 mg adalimumab administered subcutaneously every other week (eow) from Flare Week 0 to Flare Week 16 (Open-Label Rescue Period)

Reporting group title	Adalimumab Withdrawal to Rescue Arm

Reporting group description:

40 mg adalimumab administered subcutaneously every other week (eow) from Flare Week 0 to Flare Week 16 (Open-Label Rescue Period)

Subject analysis set title	Flared Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who experienced flare during the Double-blind Period

Subject analysis set title	Non-Flared Participants
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who did not experience flare during the Double-blind Period

Subject analysis set title	DAS28 (ESR) < 2.6
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Disease Activity Score 28 (DAS28 ESR) < 2.6

Subject analysis set title	SDAI ≤ 3.3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Simplified Disease Activity Index (SDAI) score ≤ 3.3

Subject analysis set title	CDAI ≤ 2.8
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Clinical Disease Activity Index (CDAI) score ≤ 2.8

Primary: Association Between a Composite of Baseline Hand and Wrist Synovitis and Bone Marrow Edema RAMRIS Scores and Flare up to Week 40 in the Tapering Arm

End point title	Association Between a Composite of Baseline Hand and Wrist Synovitis and Bone Marrow Edema RAMRIS Scores and Flare up to Week 40 in the Tapering Arm[1]

End point description:

The composite score is the sum of the baseline hand and wrist synovitis and bone marrow edema RAMRIS scores. Flare is defined as an increase from Double-blind Baseline in DAS (Disease Activity Score) 28 erythrocyte sedimentation rate (ESR) of > 0.6 AND DAS28 [ESR] > 2.6, OR an increase in DAS28 (ESR) of ≥ 1.2 irrespective of the resulting DAS28 [ESR]. The association between the composite baseline hand and wrist synovitis score and baseline bone marrow edema rheumatoid arthritis MRI scoring system (RAMRIS) score and occurrence of rheumatoid arthritis flare up to Week 40 in the Tapering arm was examined using logistic regression, and the 95% confidence interval of the odds ratio was calculated.

End point type	Primary

End point timeframe:

From Week 4 to Week 40

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Wald Chi test was performed; p=0.688

End point values	Adalimumab Tapering			
Subject group type	Reporting group			
Number of subjects analysed	102[2]			
Units: odds ratio				
number (confidence interval 95%)	0.979 (0.885 to 1.084)			

Notes:

[2] - Subjects in Tapering arm who received at least 1 dose of study drug during the Double-blind period

Statistical analyses

No statistical analyses for this end point

Primary: Association Between Baseline Bone Marrow Edema RAMRIS Score and Flare up to Week 40 in the Tapering Arm

End point title	Association Between Baseline Bone Marrow Edema RAMRIS Score and Flare up to Week 40 in the Tapering Arm[3]

End point description:

Bone marrow edema in each bone was scored separately. The scale is 0–3 based on the proportion of bone with edema, as follows—0: no edema; 1: 1–33% of bone edematous; 2: 34–66% of bone edematous; 3: 67–100%. Flare is defined as an increase from Double-blind Baseline in DAS (Disease Activity Score) 28 erythrocyte sedimentation rate (ESR) of > 0.6 AND DAS28 [ESR] > 2.6, OR an increase in DAS28 (ESR) of ≥ 1.2 irrespective of the resulting DAS28 [ESR]. The association between baseline bone marrow edema rheumatoid arthritis MRI scoring system (RAMRIS) score and occurrence of rheumatoid arthritis flare up to Week 40 in the Tapering arm was examined using logistic regression, and the 95% confidence interval of the odds ratio was calculated.

End point type	Primary

End point timeframe:

From Week 4 to Week 40

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Wald Chi test was performed; p=0.592

End point values	Adalimumab Tapering			
Subject group type	Reporting group			
Number of subjects analysed	102[4]			
Units: odd ratio				
number (confidence interval 95%)	0.959 (0.821 to 1.119)			

Notes:

[4] - Subjects in Tapering arm who received at least 1 dose of study drug during the Double-blind period

Statistical analyses

No statistical analyses for this end point

Primary: Association Between Baseline Hand and Wrist Synovitis Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Score and Flare up to Week 40 in the Tapering Arm

End point title	Association Between Baseline Hand and Wrist Synovitis Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Score and Flare up to Week 40 in the Tapering Arm[5]

End point description:

Synovitis was assessed in three wrist regions (the distal radioulnar joint; the radiocarpal joint; the intercarpal and carpometacarpal joints) and in each Metacarpophalangeal joint (MCP) joint. The first carpometacarpal joint and the first MCP joint are not scored. The scale is 0–3. Score 0 is normal, and 1–3 (mild, moderate, severe) are by thirds of the presumed maximum volume of enhancing tissue in the synovial compartment. Flare is defined as an increase from Double-blind Baseline in DAS (Disease Activity Score) 28 erythrocyte sedimentation rate (ESR) of > 0.6 AND DAS28 [ESR] > 2.6, OR an increase in DAS28 (ESR) of ≥ 1.2 irrespective of the resulting DAS28 [ESR]. The association between baseline hand and wrist synovitis RAMRIS score and occurrence of rheumatoid arthritis flare up to Week 40 in the Tapering arm was examined using logistic regression, and the 95% confidence interval of the odds ratio was calculated.

End point type	Primary

End point timeframe:

From Week 4 to Week 40

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Wald Chi test was performed; p=0.943

End point values	Adalimumab Tapering			
Subject group type	Reporting group			
Number of subjects analysed	102[6]			
Units: odds ratio				
number (confidence interval 95%)	0.993 (0.822 to 1.199)			

Notes:

[6] - Subjects in tapering arm who received at least 1 dose of study drug during the Double-blind period

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to flare

End point title	Median time to flare

End point description:

Time to flare was defined as the number of weeks from the date of the first dose of study drug in the Double-blind period to the date of flare.

End point type	Secondary

End point timeframe:

From Week 4 to Week 40

End point values	Adalimumab Tapering	Adalimumab Withdrawal Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[7]	20[8]		
Units: weeks				
median (confidence interval 95%)	999 (36.4 to 999)	999 (12.1 to 999)		

Notes:

[7] - 999 = not calculable/estimable due to an insufficient number of subjects with events

[8] - 999 = not calculable/estimable due to an insufficient number of subjects with events

Statistical analyses

No statistical analyses for this end point

Secondary: Physicians' Assessment of Flare Severity

End point title	Physicians' Assessment of Flare Severity

End point description:

Physicians rated the severity of flare at the Flare Week 0 visit from 0 (not severe) to 10 (very severe). The number of participants within each level of flare severity is presented.

End point type	Secondary

End point timeframe:

At the Flare Week 0 Visit

End point values	Adalimumab Tapering to Rescue Arm	Adalimumab Withdrawal to Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[9]	8[10]		
Units: Number of participants				
Score of 0	1	1		
Score of 1	2	0		

Score of 2	3	0		
Score of 3	3	1		
Score of 4	6	2		
Score of 5	1	1		
Score of 6	4	0		
Score of 7	1	0		
Score of 8	0	0		
Score of 9	0	0		
Score of 10	0	0		
Missing	9	3		

Notes:

[9] - Open-label-rescue-treated subjects excluding those who falsely entered the Open-label rescue period

[10] - Open-label-rescue-treated subjects excluding those who falsely entered the Open-label rescue period

Statistical analyses

No statistical analyses for this end point

Secondary: Participants' Assessment of Flare Severity

End point title	Participants' Assessment of Flare Severity

End point description:

Participants rated the severity of flare at the Flare Week 0 visit from 0 (not severe) to 10 (very severe). The number of participants within each level of flare severity is presented.

End point type	Secondary

End point timeframe:

At the Flare Week 0 Visit

End point values	Adalimumab Tapering to Rescue Arm	Adalimumab Withdrawal to Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[11]	8[12]		
Units: Number of participants				
Score of 0	1	0		
Score of 1	2	1		
Score of 2	2	2		
Score of 3	3	0		
Score of 4	4	0		
Score of 5	1	1		
Score of 6	4	1		
Score of 7	1	0		
Score of 8	2	0		
Score of 9	0	0		
Score of 10	2	0		
Missing	8	3		

Notes:

[11] - Open-label-rescue-treated subjects excluding those who falsely entered the Open-label rescue period
[12] - Open-label-rescue-treated subjects excluding those who falsely entered the Open-label rescue period

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Flare

End point title	Percentage of Participants With a Flare

End point description:

Flare was defined as an increase from Double-blind Baseline in DAS (Disease Activity Score) 28 erythrocyte sedimentation rate (ESR) of > 0.6 AND DAS28 [ESR] > 2.6, OR an increase in DAS28 (ESR) of ≥ 1.2 irrespective of the resulting DAS28 [ESR].

End point type	Secondary

End point timeframe:

From Week 4 to Week 40

End point values	Adalimumab Tapering	Adalimumab Withdrawal Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[13]	20[14]		
Units: percentage of participants				
number (confidence interval 95%)	36.3 (27.0 to 46.4)	45.0 (23.1 to 68.5)		

Notes:

[13] - Subjects who received at least 1 dose of study drug during the Double-blind period

[14] - Subjects who received at least 1 dose of study drug during the Double-blind period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Regained Clinical Remission in the Open-Label Rescue Arm Over Time

End point title	Number of Participants Who Regained Clinical Remission in the Open-Label Rescue Arm Over Time

End point description:

The Disease Activity Score 28 (DAS28) is a validated index of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, the erythrocyte sedimentation rate (ESR; mm/hour), and the participant's assessment of global disease activity (on a visual analog scale [VAS] from 0 to 10 cm) are included in the DAS28 (ESR) score. Scores on the DAS28 range from 0 to 10; higher scores indicate more disease activity. Clinical remission was defined as DAS28 (ESR) < 2.6.

End point type	Secondary

End point timeframe:

From Flare Week 0 to Flare Week 16

End point values	Adalimumab Tapering to Rescue Arm	Adalimumab Withdrawal to Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[15]	8[16]		
Units: Number of participants				
Flare Week 0 (n=30;8)	3	1		
Flare Week 4 (n= 29;7)	14	1		
Flare Week 10 (n=29;7)	17	3		
Flare Week 16 (n=29;8)	13	4		

Notes:

[15] - Open-label-rescue-treated subjects excluding those who incorrectly entered the Rescue period; LOCF

[16] - Open-label-rescue-treated subjects excluding those who incorrectly entered the Rescue period; LOCF

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Clinical Remission From the Occurrence of Flare

End point title	Median Time to Clinical Remission From the Occurrence of Flare

End point description:

The Disease Activity Score 28 (DAS28) is a validated index of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, the erythrocyte sedimentation rate (ESR; mm/hour), and the participant's assessment of global disease activity (on a visual analog scale [VAS] from 0 to 10 cm) are included in the DAS28 (ESR) score. Scores on the DAS28 range from 0 to 10; higher scores indicate more disease activity. Clinical remission was defined as DAS28 (ESR) < 2.6. Time to clinical remission was defined as the number of weeks from the occurrence of flare to the first date of clinical remission.

End point type	Secondary

End point timeframe:

From Flare Week 0 to Flare Week 16

End point values	Adalimumab Tapering to Rescue Arm	Adalimumab Withdrawal to Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[17]	8[18]		
Units: weeks				
median (confidence interval 95%)	6.1 (4.1 to 16.3)	18.0 (0.1 to 18.0)		

Notes:

[17] - Open-label-rescue-treated subjects excluding those who incorrectly entered the Rescue period

[18] - Open-label-rescue-treated subjects excluding those who incorrectly entered the Rescue period

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Disease Activity Score 28 (DAS28)

End point title	Mean Change From Double-blind Baseline in Disease Activity Score 28 (DAS28)

End point description:

The Disease Activity Score 28 (DAS28) is a validated index of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, the erythrocyte sedimentation rate (ESR; mm/hour), and the participant's assessment of global disease activity (on a visual analog scale [VAS] from 0 to 10 cm) are included in the DAS28 (ESR) score. Scores on the DAS28 range from 0 to 10; higher scores indicate more disease activity. Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[19]	76[20]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;63)	0.7 (± 1.27)	0.1 (± 0.46)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	0.1 (± 0.47)	0.1 (± 0.55)		
Double Blind Week 16- Tapering Arm (n=35;63)	1.2 (± 1.34)	0.1 (± 0.39)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	0.9 (± 0.58)	0.0 (± 0.43)		
Double Blind Week 22- Tapering Arm (n=19;63)	0.7 (± 1.18)	-0.0 (± 0.53)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	0.5 (± 0.31)	0.1 (± 0.24)		
Double Blind Week 28- Tapering Arm (n=16;63)	0.8 (± 1.16)	0.1 (± 0.50)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	1.0 (± 1.54)	0.2 (± 0.25)		
Double Blind Week 34- Tapering Arm (n=12;63)	0.7 (± 0.59)	-0.0 (± 0.54)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	-0.7 (± 0.11)	-0.0 (± 0.46)		
Double Blind Week 40- Tapering Arm (n=11;63)	1.5 (± 1.20)	0.0 (± 0.52)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	0.8 (± 2.18)	0.2 (± 0.38)		
Flare Week 0- Tapering Arm (n=30:0)	2.3 (± 1.15)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	1.9 (± 0.96)	999 (± 999)		
Flare Week 4- Tapering Arm (n=29;0)	1.3 (± 1.05)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	1.2 (± 1.14)	999 (± 999)		
Flare Week 10- Tapering Arm (n=29;0)	0.9 (± 0.81)	999 (± 999)		

Flare Week 10- Withdrawal Arm (n=7;0)	0.7 (± 0.50)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	1.2 (± 1.04)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	0.6 (± 0.80)	999 (± 999)		

Notes:

[19] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[20] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Clinical Disease Activity Index (CDAI) Score

End point title	Mean Change From Double-blind Baseline in Clinical Disease Activity Index (CDAI) Score

End point description:

The CDAI is a validated measure of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, global health assessed by the participant on a visual analogue scale from 0 to 10 (cm), and global health assessed by an investigator on a visual analogue scale from 0 to 10 (cm) were included in the CDAI score. Scores on the CDAI range from 0 to 76; higher scores indicate more disease activity. Negative values indicate improvement from the Double-blind baseline score. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[21]	76[22]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;62)	4.4 (± 7.68)	0.6 (± 1.34)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	1.0 (± 2.45)	1.4 (± 2.85)		
Double Blind Week 16- Tapering Arm (n=35;63)	7.0 (± 9.35)	0.4 (± 1.30)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	2.9 (± 2.42)	-0.1 (± 0.88)		
Double Blind Week 22- Tapering Arm (n=19;63)	3.2 (± 4.98)	0.3 (± 1.38)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	2.2 (± 1.93)	0.1 (± 0.73)		
Double Blind Week 28- Tapering Arm (n=16;63)	3.7 (± 6.19)	0.5 (± 1.37)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	6.3 (± 8.40)	-0.1 (± 0.80)		
Double Blind Week 34- Tapering Arm (n=12;63)	2.7 (± 3.04)	0.2 (± 1.08)		

Double Blind Week 34- Withdrawal Arm (n=2;11)	-0.1 (± 0.14)	0.0 (± 0.92)		
Double Blind Week 40- Tapering Arm (n=11;63)	7.4 (± 10.04)	0.1 (± 1.33)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	7.7 (± 11.38)	-0.3 (± 0.48)		
Flare Week 0- Tapering Arm (n=30;0)	12.3 (± 9.56)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	9.4 (± 9.13)	999 (± 999)		
Flare Week 4- Tapering Arm (n=28;0)	5.0 (± 6.55)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	5.4 (± 9.59)	999 (± 999)		
Flare Week 10- Tapering Arm (n=29;0)	3.5 (± 4.55)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	3.6 (± 2.52)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	4.5 (± 6.14)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	2.8 (± 4.19)	999 (± 999)		

Notes:

[21] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[22] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Simplified Disease Activity Index (SDAI) Score

End point title	Mean Change From Double-blind Baseline in Simplified Disease Activity Index (SDAI) Score

End point description:

The SDAI is a validated measure of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, global health assessed by the participant on a visual analogue scale from 0 to 10 (cm), global health assessed by an investigator on a visual analogue scale from 0 to 10 (cm), and serum levels of C-reactive protein levels (mg/dL) were included in the SDAI score. Scores on the SDAI range from 0 to 86; higher scores indicate more disease activity. Negative values indicate improvement from the Double-blind baseline score. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[23]	76[24]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=36;62)	3.7 (± 8.57)	0.8 (± 1.85)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	0.9 (± 2.59)	1.3 (± 2.67)		
Double Blind Week 16- Tapering Arm (n=35;63)	6.3 (± 10.25)	0.4 (± 1.35)		

Double Blind Week 16- Withdrawal Arm (n=9;11)	3.6 (± 2.80)	-0.1 (± 0.90)		
Double Blind Week 22- Tapering Arm (n=19;63)	3.6 (± 5.18)	0.3 (± 1.47)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	2.3 (± 1.95)	-0.0 (± 0.88)		
Double Blind Week 28- Tapering Arm (n=16;63)	3.8 (± 6.34)	0.4 (± 1.37)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	6.4 (± 8.40)	0.1 (± 1.61)		
Double Blind Week 34- Tapering Arm (n= 12;63)	3.0 (± 3.29)	0.2 (± 1.17)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.1 (± 0.33)	0.1 (± 1.07)		
Double Blind Week 40- Tapering Arm (n=11;63)	7.5 (± 10.27)	0.1 (± 1.37)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	8.5 (± 10.23)	-0.3 (± 0.62)		
Flare Week 0- Tapering Arm (n=30;0)	11.6 (± 11.17)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	9.9 (± 8.31)	999 (± 999)		
Flare Week 4- Tapering Arm (n=28;0)	4.1 (± 8.73)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	5.2 (± 9.64)	999 (± 999)		
Flare Week 10- Tapering Arm (n=29;0)	2.5 (± 7.53)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	3.5 (± 2.51)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	3.6 (± 6.63)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	2.7 (± 4.20)	999 (± 999)		

Notes:

[23] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[24] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Maintaining Clinical Remission Defined By DAS28 (ESR) < 2.6, SDAI ≤ 3.3, and CDAI ≤ 2.8 at Each Visit By Treatment Arm

End point title	Number of Participants Maintaining Clinical Remission Defined By DAS28 (ESR) < 2.6, SDAI ≤ 3.3, and CDAI ≤ 2.8 at Each Visit By Treatment Arm

End point description:

The maintenance of clinical remission after regaining remission during the Open-label rescue period was defined as either Disease Activity Score 28 (DAS28 ESR) < 2.6, Simplified Disease Activity Index (SDAI) score ≤ 3.3, or Clinical Disease Activity Index (CDAI) score ≤ 2.8). For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period.

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	DAS28 (ESR) < 2.6	SDAI ≤ 3.3	CDAI ≤ 2.8	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	122[25]	122[26]	122[27]	
Units: Number of participants				
Double Blind Baseline- Tapering Arm (n=102;102;102	102	89	85	
Double Blind Baseline- Withdrawal Arm (n=20;20;20)	20	19	19	
Double Blind Week 10- Tapering Arm (n=100;98;99)	85	63	62	
Double Blind Week 10- Withdrawal Arm (n=20;20;20)	18	16	14	
Double Blind Week 16- Tapering Arm (n=98;98;98)	78	64	62	
Double Blind Week 16- Withdrawal Arm (n=20;20;20)	15	13	15	
Double Blind Week 22- Tapering Arm (n=82,82,82)	75	59	58	
Double Blind Week 22- Withdrawal Arm (n=15;15;15)	14	13	13	
Double Blind Week 28- Tapering Arm (n= 79;79;79)	69	58	57	
Double Blind Week 28- Withdrawal Arm (n=15;15;15)	13	12	13	
Double Blind Week 34- Tapering Arm (n=75;75;75)	70	58	58	
Double Blind Week 34- Withdrawal Arm (n=13;13;13)	13	13	13	
Double Blind Week 40- Tapering Arm (n=74;74;74)	64	57	56	
Double Blind Week 40- Withdrawal Arm (n=13;13;13)	11	12	12	
Flare Week 0- Tapering Arm (n=31;31;31)	4	4	4	
Flare Week 0- Withdrawal Arm (n=8;8;8)	1	0	2	
Flare Week 4- Tapering Arm (n=29;28;28)	14	13	13	
Flare Week 4- Withdrawal Arm (n=7;7;7)	1	2	2	
Flare Week 10- Tapering Arm (n=29;29;29)	17	14	14	
Flare Week 10- Withdrawal Arm (n=7;7;7)	3	2	2	
Flare Week 16- Tapering Arm (n=29;29;29)	13	13	13	
Flare Week 16- Withdrawal Arm (n=8;8;8)	4	4	4	

Notes:

[25] - Subjects who received at least 1 dose of study drug during the Double-blind period; LOCF

[26] - Subjects who received at least 1 dose of study drug during the Double-blind period; LOCF

[27] - Subjects who received at least 1 dose of study drug during the Double-blind period; LOCF

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline to Week 40 or Final Visit in Magnetic Resonance Imaging (MRI) Synovitis Score

End point title	Mean Change From Double-blind Baseline to Week 40 or Final Visit in Magnetic Resonance Imaging (MRI) Synovitis Score

End point description:

Synovitis was assessed in three wrist regions (the distal radioulnar joint; the radiocarpal joint; the intercarpal and carpometacarpal joints) and in each Metacarpophalangeal joint (MCP) joint. The first carpometacarpal joint and the first MCP joint are not scored. The scale is 0–3. Score 0 is normal, and 1–3 (mild, moderate, severe) are by thirds of the presumed maximum volume of enhancing tissue in the synovial compartment. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data; 9999= not calculable/estimable due to an insufficient number of subjects with an observation

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 or Final visit

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45[28]	76[29]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 40- Tapering Arm (n=6;51)	-0.1 (± 1.20)	0.1 (± 1.33)		
Double Blind Week 40- Withdrawal Arm (n=1;10)	0.0 (± 9999)	-0.1 (± 0.90)		
Flare Week 16- Tapering Arm (n=25;0)	0.8 (± 1.84)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	0.1 (± 1.81)	999 (± 999)		

Notes:

[28] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[29] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline to Week 40 or Final Visit in Bone Marrow Edema (BME) Score

End point title	Mean Change From Double-blind Baseline to Week 40 or Final Visit in Bone Marrow Edema (BME) Score

End point description:

Bone edema in each bone was scored separately. The scale is 0–3 based on the proportion of bone with edema, as follows—0: no edema; 1: 1–33% of bone edematous; 2: 34–66% of bone edematous; 3: 67–100%. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data; 9999= not calculable/estimable due to an insufficient number of subjects with an observation

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 or Final visit

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[30]	76[31]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 40- Tapering Arm (n=6;52)	-0.5 (± 0.84)	0.0 (± 1.07)		
Double Blind Week 40- Withdrawal Arm (n=1;10)	0.0 (± 9999)	1.2 (± 3.52)		
Flare Week 16- Tapering Arm (n=26;0)	-0.1 (± 0.47)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	0.3 (± 0.38)	999 (± 999)		

Notes:

[30] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[31] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline to Week 40 or Final Visit in Bone Erosions Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Score

End point title	Mean Change From Double-blind Baseline to Week 40 or Final Visit in Bone Erosions Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS) Score

End point description:

Bone erosions in each bone (wrists: carpal bones, distal radius, distal ulna, metacarpal bases; MCP joints: metacarpal heads, phalangeal bases) were scored separately. The scale is 0–10, based on the proportion of eroded bone compared to the ''assessed bone volume'', judged on all available images—0: no erosion; 1: 1–10% of bone eroded; 2; 11–20%, etc. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data; 9999= not calculable/estimable due to an insufficient number of subjects with an observation

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 or Final Visit

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[32]	76[33]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 40- Tapering Arm (n=6;52)	-0.5 (± 1.73)	0.1 (± 0.52)		

Double Blind Week 40- Withdrawal Arm (n=1;10)	-2.0 (± 9999)	0.0 (± 1.08)		
Flare Week 16- Tapering Arm (n=26;0)	0.3 (± 1.02)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	0.1 (± 0.88)	999 (± 999)		

Notes:

[32] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[33] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Health Assessment Questionnaire- Disability Index (HAQ-DI) Score Over Time

End point title	Mean Change From Double-blind Baseline in Health Assessment Questionnaire- Disability Index (HAQ-DI) Score Over Time

End point description:

The Health Assessment Questionnaire - Disability Index (HAQ-DI) is a questionnaire specific for rheumatoid arthritis. It consists of 20 questions over 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and daily activities. Subjects assessed their ability to do each task over the past week using the categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task were summed and averaged to provide an overall score ranging from 0 to 3, where 0 represents no disability and 3 very severe, high-dependency disability. The minimal clinically important difference (MCID) defined for the HAQ-DI is ≥ 0.22. For Double-blind period data, missing values were only imputed up to the time when the subject entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data; 9999= not calculable/estimable due to an insufficient number of subjects with an observation

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[34]	76[35]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=30;62)	0.1 (± 0.3)	0.0 (± 0.18)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	0.3 (± 0.61)	0.0 (± 0.17)		
Double Blind Week 16- Tapering Arm (n=19;63)	0.2 (± 0.40)	-0.0 (± 0.28)		
Double Blind Week 16- Withdrawal Arm (n=5;11)	0.3 (± 0.54)	-0.0 (± 0.12)		
Double Blind Week 22- Tapering Arm (n=15;63)	0.1 (± 0.37)	-0.0 (± 0.26)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	0.4 (± 0.79)	0.1 (± 0.39)		
Double Blind Week 28- Tapering Arm (n=12;63)	0.2 (± 0.43)	-0.0 (± 0.27)		
Double Blind Week 28- Withdrawal Arm (n=3;11)	0.7 (± 0.69)	-0.1 (± 0.15)		

Double Blind Week 34- Tapering Arm (n=11;63)	0.3 (± 0.49)	-0.0 (± 0.30)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.2 (± 0.27)	0.1 (± 0.17)		
Double Blind Week 40- Tapering Arm (n=7;63)	0.4 (± 0.40)	-0.1 (± 0.33)		
Double Blind Week 40- Withdrawal Arm (n=1;11)	1.9 (± 9999)	0.0 (± 0.16)		
Flare Week 0- Tapering Arm (n=25;0)	0.4 (± 0.57)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=7;0)	0.3 (± 0.29)	999 (± 999)		
Flare Week 4- Tapering Arm (n=27;0)	0.2 (± 0.49)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	0.2 (± 0.35)	999 (± 999)		
Flare Week 10- Tapering Arm (n=27;0)	0.1 (± 0.24)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	0.1 (± 0.20)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	0.2 (± 0.39)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	0.1 (± 0.24)	999 (± 999)		

Notes:

[34] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[35] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Health Assessment Questionnaire-Disability Index (HAQ-DI) Score ≤ 0.5 at Double-blind Baseline and at Week 40

End point title	Number of Participants With Health Assessment Questionnaire-Disability Index (HAQ-DI) Score ≤ 0.5 at Double-blind Baseline and at Week 40

End point description:

The Health Assessment Questionnaire - Disability Index (HAQ-DI) is a participant-reported questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and daily activities. Participants assessed their ability to do each task over the past week using the following response categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task were summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. The number of participants with HAQ-DI score ≤ 0.5 (considered to be normal) was recorded.

End point type	Secondary

End point timeframe:

Week 4 and Week 40

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[36]	76[37]		
Units: Number of participants				
Double Blind Week 4- Tapering Arm (n=37;65)	21	50		
Double Blind Week 4- Withdrawal Arm (n=9;11)	7	10		

Double Blind Week 40- Tapering Arm (n=7;63)	2	48		
Double Blind Week 40- Withdrawal Arm (n=1;11)	0	9		

Notes:

[36] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[37] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Routine Assessment of Patient Index Data (RAPID3) Questionnaire Scores Assessed During In-office Visits

End point title	Mean Change From Double-blind Baseline in Routine Assessment of Patient Index Data (RAPID3) Questionnaire Scores Assessed During In-office Visits

End point description:

The RAPID3 is an activity index derived from the Multi-dimensional Health Assessment Questionnaire (MD-HAQ). It includes an assessment of physical function, a pain Visual Analog Scale (VAS), and a participant global assessment of disease activity VAS. The total RAPID3 score ranges from 0 to 30 where higher scores represent severe disease. Negative values indicate improvement from the Double-blind baseline score. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[38]	76[39]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;63)	1.9 (± 3.92)	0.7 (± 3.20)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	1.4 (± 3.73)	1.5 (± 4.67)		
Double Blind Week 16- Tapering Arm (n=35;63)	4.7 (± 5.66)	0.8 (± 2.80)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	2.5 (± 4.59)	0.1 (± 1.37)		
Double Blind Week 22- Tapering Arm (n=19;63)	2.6 (± 4.83)	0.3 (± 2.83)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	3.6 (± 4.18)	0.6 (± 3.31)		
Double Blind Week 28- Tapering Arm (n=16;63)	2.2 (± 4.20)	0.6 (± 2.47)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	3.7 (± 4.45)	-0.3 (± 1.61)		
Double Blind Week 34- Tapering Arm (n=12;63)	2.2 (± 3.77)	-0.0 (± 1.93)		

Double Blind Week 34- Withdrawal Arm (n=2;11)	1.9 (± 2.62)	1.6 (± 2.33)		
Double Blind Week 40- Tapering Arm (n=11;63)	4.7 (± 6.22)	0.0 (± 2.39)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	0.4 (± 0.92)	0.8 (± 1.62)		
Flare Week 0- Tapering Arm (n=30;0)	6.1 (± 6.64)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	3.9 (± 5.60)	999 (± 999)		
Flare Week 4- Tapering Arm (n=27;0)	3.1 (± 5.38)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	3.2 (± 4.15)	999 (± 999)		
Flare Week 10- Tapering Arm (n=27;0)	2.8 (± 3.93)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	2.3 (± 2.61)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	2.9 (± 4.22)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	2.1 (± 3.01)	999 (± 999)		

Notes:

[38] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[39] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Flare Week 0 in Routine Assessment of Patient Index Data (RAPID3) Questionnaire Scores Assessed at Home

End point title	Mean Change From Flare Week 0 in Routine Assessment of Patient Index Data (RAPID3) Questionnaire Scores Assessed at Home

End point description:

The RAPID3 is an activity index derived from the Multi-dimensional Health Assessment Questionnaire (MD-HAQ). It includes an assessment of physical function, a pain Visual Analog Scale (VAS), and a participant global assessment of disease activity VAS. The total RAPID3 score ranges from 0 to 30 where higher scores represent severe disease. Negative values indicate improvement from the Double-blind baseline score.

End point type	Secondary

End point timeframe:

Flare Week 0 and Flare Weeks 1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15

End point values	Flared Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	33[40]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Flare Week 1- Tapering Arm (n=19)	-1.6 (± 4.92)			
Flare Week 1- Withdrawal Arm (n=3)	3.7 (± 7.20)			
Flare Week 2- Tapering Arm (n=22)	-3.1 (± 5.41)			
Flare Week 2- Withdrawal Arm (n=4)	0.8 (± 6.89)			
Flare Week 3- Tapering Arm (n=25)	-3.8 (± 6.78)			
Flare Week 3- Withdrawal Arm (n=6)	-0.4 (± 7.94)			
Flare Week 5- Tapering Arm (n=26)	-3.8 (± 6.61)			

Flare Week 5- Withdrawal Arm (n=6)	-0.8 (± 6.56)			
Flare Week 6- Tapering Arm (n=26)	-4.1 (± 6.81)			
Flare Week 6- Withdrawal Arm (n=6)	-0.9 (± 6.97)			
Flare Week 7- Tapering Arm (n=26)	-3.7 (± 6.86)			
Flare Week 7- Withdrawal Arm (n=6)	-0.6 (± 6.26)			
Flare Week 8- Tapering Arm (n=27)	-4.4 (± 7.17)			
Flare Week 8- Withdrawal Arm (n=6)	-0.6 (± 5.56)			
Flare Week 9- Tapering Arm (n=27)	-3.3 (± 5.81)			
Flare Week 9- Withdrawal Arm (n=6)	-1.0 (± 5.89)			
Flare Week 11- Tapering Arm (n=27)	-3.7 (± 5.69)			
Flare Week 11- Withdrawal Arm (n=6)	-1.0 (± 5.85)			
Flare Week 12- Tapering Arm (n=27)	-3.4 (± 5.84)			
Flare Week 12- Withdrawal Arm (n=6)	-2.3 (± 4.46)			
Flare Week 13- Tapering Arm (n=27)	-3.5 (± 5.72)			
Flare Week 13- Withdrawal Arm (n=6)	-2.5 (± 4.78)			
Flare Week 14- Tapering Arm (n=27)	-3.1 (± 5.54)			
Flare Week 14- Withdrawal Arm (n=6)	-2.4 (± 4.79)			
Flare Week 15- Tapering Arm (n=27)	-3.5 (± 6.69)			
Flare Week 15- Withdrawal Arm (n=6)	-2.2 (± 4.70)			

Notes:

[40] - Open-label-rescue-treated subjects with available data; last observation carried forward

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Swollen Joint Count 28

End point title	Mean Change From Double-blind Baseline in Swollen Joint Count 28

End point description:

Twenty-eight joints, excluding hip joints, were assessed for swelling by physical examination. Swelling of each joint was classified as present (1) or absent (0), for a total possible score of 0 (0 joints with swelling) to 28 (worst possible score/28 joints with swelling). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[41]	76[42]		
Units: swollen joint counts				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;64)	0.9 (± 2.09)	0.1 (± 0.58)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	0.1 (± 0.33)	-0.1 (± 0.30)		

Double Blind Week 16- Tapering Arm (n=35;63)	1.2 (± 2.15)	-0.0 (± 0.34)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	0.3 (± 0.50)	0.0 (± 0.45)		
Double Blind Week 22- Tapering Arm (n=19;63)	0.6 (± 1.64)	0.1 (± 0.64)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	0.5 (± 0.58)	-0.1 (± 0.30)		
Double Blind Week 28- Tapering Arm (n=16;63)	0.5 (± 0.89)	0.0 (± 0.33)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	2.0 (± 2.45)	-0.1 (± 0.30)		
Double Blind Week 34- Tapering Arm (n=12;63)	0.0 (± 0.43)	0.0 (± 0.46)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.0 (± 0.00)	-0.1 (± 0.30)		
Double Blind Week 40- Tapering Arm (n=11;63)	1.5 (± 3.01)	0.0 (± 0.42)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	2.0 (± 2.83)	-0.1 (± 0.30)		
Flare Week 0- Tapering Arm (n=30;0)	2.3 (± 2.60)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	1.9 (± 2.10)	999 (± 999)		
Flare Week 4- Tapering Arm (n=30;0)	1.2 (± 1.98)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=8;0)	0.6 (± 1.06)	999 (± 999)		
Flare Week 10- Tapering Arm (n=30;0)	0.4 (± 0.89)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=8;0)	0.1 (± 0.35)	999 (± 999)		
Flare Week 16- Tapering Arm (n=30;0)	0.9 (± 1.81)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	0.3 (± 0.46)	999 (± 999)		

Notes:

[41] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[42] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Swollen Joint Count 66

End point title	Mean Change From Double-blind Baseline in Swollen Joint Count 66

End point description:

Sixty-six joints were assessed for swelling by physical examination. Swelling of each joint was classified as present (1) or absent (0), for a total possible score of 0 (0 joints with swelling) to 66 (worst possible score/66 joints with swelling). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[43]	76[44]		
Units: swollen joint counts				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;64)	1.1 (± 2.36)	0.1 (± 0.67)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	0.1 (± 0.33)	-0.2 (± 0.40)		
Double Blind Week 16- Tapering Arm (n=35;63)	1.4 (± 2.56)	-0.0 (± 0.34)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	0.4 (± 0.53)	0.0 (± 0.45)		
Double Blind Week 22- Tapering Arm (n=19;63)	0.6 (± 1.64)	0.1 (± 0.73)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	1.0 (± 1.41)	-0.1 (± 0.30)		
Double Blind Week 28- Tapering Arm (n=16;63)	0.5 (± 0.89)	0.1 (± 0.66)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	3.3 (± 4.72)	-0.2 (± 0.40)		
Double Blind Week 34- Tapering Arm (n=12;63)	0.0 (± 0.43)	0.0 (± 0.54)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.0 (± 0.00)	-0.2 (± 0.40)		
Double Blind Week 40- Tapering Arm (n=11;63)	1.5 (± 3.01)	0.0 (± 0.46)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	2.0 (± 2.83)	-0.2 (± 0.40)		
Flare Week 0- Tapering Arm (n=30;0)	2.6 (± 2.90)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	2.6 (± 3.38)	999 (± 999)		
Flare Week 4- Tapering Arm (n=30;0)	1.3 (± 1.99)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=8;0)	0.6 (± 1.06)	999 (± 999)		
Flare Week 10- Tapering Arm (n=30;0)	0.6 (± 1.10)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=8;0)	0.4 (± 0.52)	999 (± 999)		
Flare Week 16- Tapering Arm (n=30;0)	1.1 (± 2.21)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	0.4 (± 0.74)	999 (± 999)		

Notes:

[43] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[44] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Tender Joint Count 28

End point title	Mean Change From Double-blind Baseline in Tender Joint Count 28

End point description:

Twenty-eight joints were assessed for tenderness by physical examination. Pain or tenderness of each joint was classified as present (1) or absent (0), for a total possible score of 0 (0 joints with tenderness) to 28 (worst possible score/28 joints with tenderness). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[45]	76[46]		
Units: tender joint counts				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;64)	1.3 (± 2.74)	0.1 (± 0.54)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	-0.1 (± 0.60)	0.5 (± 1.21)		
Double Blind Week 16- Tapering Arm (n=35;63)	2.5 (± 4.49)	0.1 (± 0.41)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	1.0 (± 0.87)	0.0 (± 0.00)		
Double Blind Week 22- Tapering Arm (n=19;63)	0.9 (± 1.66)	-0.0 (± 0.42)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	0.8 (± 1.50)	0.1 (± 0.30)		
Double Blind Week 28- Tapering Arm (n=16;63)	1.6 (± 3.39)	0.0 (± 0.51)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	1.8 (± 2.36)	0.2 (± 0.40)		
Double Blind Week 34- Tapering Arm (n=12;63)	1.0 (± 1.65)	-0.0 (± 0.42)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.0 (± 0.00)	0.0 (± 0.00)		
Double Blind Week 40- Tapering Arm (n=11;63)	2.0 (± 2.65)	0.0 (± 0.51)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	3.5 (± 4.95)	0.0 (± 0.00)		
Flare Week 0- Tapering Arm (n=30;0)	4.4 (± 4.63)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	3.6 (± 3.81)	999 (± 999)		
Flare Week 4- Tapering Arm (n=30;0)	1.5 (± 2.27)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=8;0)	2.5 (± 5.13)	999 (± 999)		
Flare Week 10- Tapering Arm (n=30;0)	0.9 (± 1.84)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=8;0)	1.1 (± 1.46)	999 (± 999)		
Flare Week 16- Tapering Arm (n=30;0)	1.8 (± 2.64)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	1.1 (± 1.89)	999 (± 999)		

Notes:

[45] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[46] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Tender Joint Count 68

End point title	Mean Change From Double-blind Baseline in Tender Joint Count

	68

End point description:

Sixty-eight joints were assessed for tenderness by physical examination. Pain or tenderness of each joint was classified as present (1) or absent (0), for a total possible score of 0 (0 joints with tenderness) to 68 (worst possible score/68 joints with tenderness). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[47]	76[48]		
Units: tender joint counts				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;64)	1.9 (± 3.45)	0.3 (± 1.47)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	0.1 (± 0.60)	0.9 (± 1.64)		
Double Blind Week 16- Tapering Arm (n=35;63)	3.5 (± 6.33)	0.2 (± 1.36)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	1.4 (± 1.13)	0.2 (± 0.60)		
Double Blind Week 22- Tapering Arm (n=19;63)	1.2 (± 2.27)	0.2 (± 1.35)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	2.0 (± 2.83)	0.4 (± 1.03)		
Double Blind Week 28- Tapering Arm (n=16;63)	2.5 (± 5.34)	0.1 (± 0.96)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	3.8 (± 4.50)	0.3 (± 0.47)		
Double Blind Week 34- Tapering Arm (n=12;63)	1.9 (± 2.87)	0.0 (± 0.73)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.0 (± 0.00)	0.1 (± 0.30)		
Double Blind Week 40- Tapering Arm (n=11;63)	3.0 (± 4.24)	0.0 (± 0.68)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	9.0 (± 12.73)	-0.1 (± 0.30)		
Flare Week 0- Tapering Arm (n=30;0)	6.2 (± 6.93)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	6.1 (± 6.27)	999 (± 999)		
Flare Week 4- Tapering Arm (n=30;0)	1.9 (± 2.50)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=8;0)	4.1 (± 8.48)	999 (± 999)		
Flare Week 10- Tapering Arm (n=30;0)	1.5 (± 2.69)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=8;0)	2.3 (± 2.31)	999 (± 999)		
Flare Week 16- Tapering Arm (n=30;0)	2.1 (± 3.37)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	1.6 (± 1.85)	999 (± 999)		

Notes:

[47] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[48] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Participant's Global Assessment of Disease Activity

End point title	Mean Change From Double-blind Baseline in Participant's Global Assessment of Disease Activity

End point description:

Participants rated the severity of their rheumatoid arthritis symptoms and how well they were doing during the last 24 hours by placing a vertical mark on a line with a range of 0 (very well) to 100 mm (very poorly). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[49]	76[50]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;63)	11.6 (± 19.0)	2.6 (± 8.49)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	8.0 (± 21.66)	9.6 (± 20.27)		
Double Blind Week 16- Tapering Arm (n=35;63)	20.5 (± 26.97)	2.4 (± 9.27)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	10.7 (± 19.97)	-0.3 (± 5.76)		
Double Blind Week 22- Tapering Arm (n=19;63)	10.7 (± 17.74)	1.7 (± 9.14)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	5.8 (± 8.73)	0.2 (± 8.87)		
Double Blind Week 28- Tapering Arm (n=16;63)	9.4 (± 21.03)	2.7 (± 10.03)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	15.0 (± 25.76)	-1.0 (± 7.82)		
Double Blind Week 34- Tapering Arm (n=12;63)	11.5 (± 13.70)	1.2 (± 7.23)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	-1.0 (± 1.41)	0.7 (± 7.25)		
Double Blind Week 40- Tapering Arm (n=11;63)	22.9 (± 35.32)	0.0 (± 7.60)		

Double Blind Week 40- Withdrawal Arm (n=2;11)	2.0 (± 9.90)	-1.7 (± 4.45)		
Flare Week 0- Tapering Arm (n=30;0)	29.5 (± 29.43)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	21.6 (± 27.07)	999 (± 999)		
Flare Week 4- Tapering Arm (n=29;0)	13.7 (± 22.93)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	11.7 (± 21.96)	999 (± 999)		
Flare Week 10- Tapering Arm (n=29;0)	11.7 (± 16.89)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	14.1 (± 10.35)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	9.4 (± 13.47)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	6.9 (± 9.31)	999 (± 999)		

Notes:

[49] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[50] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Participant's Global Assessment of Rheumatoid Arthritis Pain

End point title	Mean Change From Double-blind Baseline in Participant's Global Assessment of Rheumatoid Arthritis Pain

End point description:

Participants rated the severity of their rheumatoid arthritis pain in the past week by placing a vertical mark on a line with a range of 0 (no pain) to 100 mm (severe pain). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[51]	76[52]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;63)	8.0 (± 17.96)	3.5 (± 14.33)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	6.4 (± 19.05)	9.3 (± 21.04)		
Double Blind Week 16- Tapering Arm (n=35;63)	17.8 (± 27.16)	3.0 (± 12.48)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	10.7 (± 18.93)	-0.6 (± 9.65)		
Double Blind Week 22- Tapering Arm (n=19;63)	10.4 (± 19.55)	0.3 (± 7.82)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	4.0 (± 4.90)	-1.1 (± 11.20)		

Double Blind Week 28- Tapering Arm (n=16;63)	8.3 (± 17.57)	1.6 (± 9.83)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	14.0 (± 24.59)	-1.4 (± 10.93)		
Double Blind Week 34- Tapering Arm (n=12;63)	11.6 (± 14.61)	-0.3 (± 7.61)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	-3.5 (± 2.12)	2.1 (± 8.40)		
Double Blind Week 40- Tapering Arm (n=11;63)	24.0 (± 32.67)	-0.5 (± 10.00)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	-0.5 (± 20.51)	-0.9 (± 5.07)		
Flare Week 0- Tapering Arm (n=30;0)	24.4 (± 31.66)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	17.0 (± 19.38)	999 (± 999)		
Flare Week 4- Tapering Arm (n=29;0)	9.0 (± 21.68)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	11.1 (± 17.46)	999 (± 999)		
Flare Week 10- Tapering Arm (n=29;0)	7.5 (± 14.93)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	8.3 (± 9.60)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	8.0 (± 14.41)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	4.3 (± 6.32)	999 (± 999)		

Notes:

[51] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[52] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Physician's Global Assessment of Disease Activity

End point title	Mean Change From Double-blind Baseline in Physician's Global Assessment of Disease Activity

End point description:

Physicians assessed participants' current rheumatoid arthritis disease activity at the time of the visit (independent of the participant's self-assessment) by placing a vertical mark on a line with a range of 0 (very low) to 100 mm (very high). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[53]	76[54]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;62)	10.2 (± 19.54)	1.3 (± 4.27)		

Double Blind Week 10- Withdrawal Arm (n=9;11)	1.6 (± 4.67)	0.5 (± 4.74)		
Double Blind Week 16- Tapering Arm (n=35;63)	13.2 (± 21.48)	0.9 (± 5.07)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	5.0 (± 3.35)	-0.5 (± 2.98)		
Double Blind Week 22- Tapering Arm (n=19;63)	6.9 (± 14.83)	0.9 (± 5.05)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	3.8 (± 2.87)	0.4 (± 3.26)		
Double Blind Week 28- Tapering Arm (n=16;63)	7.3 (± 16.51)	1.7 (± 5.51)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	10.0 (± 10.89)	-0.9 (± 2.74)		
Double Blind Week 34- Tapering Arm (n=12;63)	5.5 (± 12.27)	0.8 (± 3.60)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.0 (± 0.00)	0.6 (± 4.13)		
Double Blind Week 40- Tapering Arm (n=11;63)	16.2 (± 26.91)	1.0 (± 5.32)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	19.5 (± 26.16)	-0.6 (± 2.42)		
Flare Week 0- Tapering Arm (n=30;0)	26.5 (± 23.28)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	17.4 (± 15.37)	999 (± 999)		
Flare Week 4- Tapering Arm (n=29;0)	12.2 (± 17.06)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	9.3 (± 20.27)	999 (± 999)		
Flare Week 10- Tapering Arm (n=30;0)	10.2 (± 13.82)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	12.9 (± 11.51)	999 (± 999)		
Flare Week 16- Tapering Arm (n=30;0)	8.6 (± 12.48)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	7.6 (± 20.00)	999 (± 999)		

Notes:

[53] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[54] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Morning Stiffness Duration

End point title	Mean Change From Double-blind Baseline in Morning Stiffness Duration

End point description:

The duration of morning stiffness was reported by participants as the average daily length during the past week in minutes (from time of awaking to time of maximal improvement). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45[55]	74[56]		
Units: minutes				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=36;62)	3.5 (± 17.33)	1.8 (± 7.19)		
Double Blind Week 10- Withdrawal Arm (n=8;10)	1.1 (± 3.60)	1.5 (± 5.97)		
Double Blind Week 16- Tapering Arm (n=34;61)	6.6 (± 24.41)	2.3 (± 12.54)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	9.2 (± 19.78)	-0.6 (± 5.05)		
Double Blind Week 22- Tapering Arm (n=18;61)	-1.6 (± 8.07)	1.5 (± 9.67)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	1.0 (± 2.00)	0.5 (± 3.70)		
Double Blind Week 28- Tapering Arm (n=15;61)	2.6 (± 13.09)	2.4 (± 10.53)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	17.3 (± 28.81)	0.0 (± 3.71)		
Double Blind Week 34- Tapering Arm (n=12;61)	0.6 (± 10.97)	1.4 (± 8.86)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.0 (± 0.00)	-1.1 (± 6.64)		
Double Blind Week 40- Tapering Arm (n=11;61)	2.0 (± 12.49)	0.4 (± 9.33)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	0.0 (± 0.00)	-0.2 (± 5.78)		
Flare Week 0- Tapering Arm (n=29;0)	13.5 (± 25.21)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	18.5 (± 26.25)	999 (± 999)		
Flare Week 4- Tapering Arm (n=29;0)	25.0 (± 110.77)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=8;0)	19.9 (± 26.51)	999 (± 999)		
Flare Week 10- Tapering Arm (n=29;0)	8.1 (± 30.20)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=8;0)	7.9 (± 9.72)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	17.3 (± 36.46)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	9.6 (± 20.65)	999 (± 999)		

Notes:

[55] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[56] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Morning Stiffness Severity

End point title	Mean Change From Double-blind Baseline in Morning Stiffness Severity

End point description:

Morning stiffness severity was assessed by a numeric rating-scale (NRS). Participants rated the severity of morning stiffness during the past week from 0 to 10 with 0 representing "not severe" and 10 "very severe". Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[57]	76[58]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;63)	0.6 (± 1.51)	0.4 (± 1.01)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	0.4 (± 1.81)	0.6 (± 1.29)		
Double Blind Week 16- Tapering Arm (n=35;63)	0.8 (± 1.73)	0.3 (± 1.11)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	0.7 (± 2.24)	-0.1 (± 1.04)		
Double Blind Week 22- Tapering Arm (n=19;63)	0.9 (± 1.27)	0.2 (± 0.85)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	0.8 (± 0.96)	0.4 (± 1.75)		
Double Blind Week 28- Tapering Arm (n=16;63)	0.9 (± 1.69)	0.2 (± 1.10)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	1.3 (± 2.75)	-0.2 (± 0.87)		
Double Blind Week 34- Tapering Arm (n=12;63)	1.3 (± 1.71)	0.1 (± 0.85)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	0.0 (± 1.41)	-0.2 (± 1.08)		
Double Blind Week 40- Tapering Arm (n=11;63)	1.8 (± 2.52)	0.1 (± 0.94)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	-1.0 (± 1.41)	-0.4 (± 1.03)		
Flare Week 0- Tapering Arm (n=30;0)	1.6 (± 2.11)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	0.9 (± 1.96)	999 (± 999)		
Flare Week 4- Tapering Arm (n=29;0)	0.8 (± 2.21)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	0.6 (± 1.72)	999 (± 999)		
Flare Week 10- Tapering Arm (n=29;0)	0.6 (± 1.40)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	0.6 (± 1.27)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	0.6 (± 1.45)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	-0.1 (± 1.13)	999 (± 999)		

Notes:

[57] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[58] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Participant's Assessment of Sleep Disturbance

End point title	Mean Change From Double-blind Baseline in Participant's Assessment of Sleep Disturbance

End point description:

Participants rated the severity of their sleep disturbance in the past week by placing a vertical mark on a line with a range of 0 (sleep is no problem) to 100 mm (sleep is a major problem). Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[59]	76[60]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;63)	2.1 (± 15.37)	0.0 (± 8.99)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	-3.2 (± 29.39)	0.8 (± 1.54)		
Double Blind Week 16- Tapering Arm (n= 35;63)	10.2 (± 19.12)	1.7 (± 15.96)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	7.1 (± 22.42)	1.1 (± 3.02)		
Double Blind Week 22- Tapering Arm (n=19;63)	8.2 (± 19.59)	-0.3 (± 10.91)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	8.3 (± 31.35)	3.5 (± 8.70)		
Double Blind Week 28- Tapering Arm (n=16;63)	1.8 (± 27.81)	2.1 (± 12.67)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	4.5 (± 19.82)	-1.0 (± 7.63)		
Double Blind Week 34- Tapering Arm (n=12;63)	5.6 (± 22.99)	-0.4 (± 11.48)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	-0.5 (± 30.41)	-0.4 (± 2.77)		
Double Blind Week 40- Tapering Arm (n=11;63)	17.7 (± 34.04)	-0.2 (± 12.40)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	-8.0 (± 15.56)	-1.0 (± 4.43)		
Flare Week 0- Tapering Arm (n=30;0)	18.9 (± 26.53)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	4.0 (± 14.61)	999 (± 999)		
Flare Week 4- Tapering Arm (n=29;0)	4.9 (± 24.33)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=7;0)	1.6 (± 10.05)	999 (± 999)		
Flare Week 10- Tapering Arm (n=29;0)	0.2 (± 21.26)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	3.9 (± 12.98)	999 (± 999)		
Flare Week 16- Tapering Arm (n=29;0)	2.3 (± 20.17)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	-7.3 (± 14.14)	999 (± 999)		

Notes:

[59] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[60] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Effectiveness Score

End point title	Mean Change From Double-blind Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Effectiveness Score

End point description:

Participants completed the 14-item Treatment Satisfaction Questionnaire for Medication (TSQM; Version 1.4) to assess satisfaction with their current rheumatoid arthritis treatment over the previous 2-3 weeks or since the last time that they took the medication. The TSQM consists of fourteen items over four domains (effectiveness, side effects, convenience, and global satisfaction). The 14 questions are answered either with yes/no or by means of a five or seven stage scale (ranging from very unsatisfied to satisfied). TSQM Scale scores for each domain range from 0 to 100 and higher scores represent higher satisfaction. Negative values indicate worsening from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

At Weeks 4, 16, 28, and 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[61]	74[62]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 16- Tapering Arm (n=35;61)	-8.3 (± 35.30)	0.2 (± 23.74)		
Double Blind Week 16- Withdrawal Arm (n=8;11)	2.8 (± 39.51)	-13.6 (± 43.84)		
Double Blind Week 28- Tapering Arm (n=16;61)	-10.1 (± 24.28)	-3.8 (± 17.82)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	-5.6 (± 45.59)	-17.2 (± 30.48)		
Double Blind Week 40- Tapering Arm (n=11;61)	-15.2 (± 33.53)	-4.4 (± 27.82)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	-19.4 (± 27.50)	-16.2 (± 45.10)		
Flare Week 0- Tapering Arm (n=28;0)	-10.9 (± 39.82)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=7;0)	-9.5 (± 38.05)	999 (± 999)		
Flare Week 4- Tapering Arm (n=25;0)	-17.3 (± 40.07)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=6;0)	-6.5 (± 48.23)	999 (± 999)		

Flare Week 10- Tapering Arm (n=27;0)	-10.7 (± 44.07)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	7.9 (± 34.23)	999 (± 999)		
Flare Week 16- Tapering Arm (n=28;0)	-7.5 (± 25.49)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	-16.7 (± 39.67)	999 (± 999)		

Notes:

[61] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[62] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Side Effects Score

End point title	Mean Change From Double-blind Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Side Effects Score

End point description:

Participants completed the 14-item Treatment Satisfaction Questionnaire for Medication (TSQM; Version 1.4) to assess satisfaction with their current rheumatoid arthritis treatment over the previous 2-3 weeks or since the last time that they took the medication. The TSQM consists of fourteen items over four domains (effectiveness, side effects, convenience, and global satisfaction). The 14 questions are answered either with yes/no or by means of a five or seven stage scale (ranging from very unsatisfied to satisfied). TSQM Scale scores for each domain range from 0 to 100 and higher scores represent higher satisfaction. Negative values indicate worsening from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

At Weeks 4, 16, 28, and 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[63]	74[64]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 16- Tapering Arm (n=35;61)	-8.0 (± 17.25)	-0.5 (± 11.26)		
Double Blind Week 16- Withdrawal Arm (n=8;11)	9.4 (± 20.04)	2.8 (± 9.42)		
Double Blind Week 28- Tapering Arm (n=16;61)	-2.7 (± 12.28)	1.1 (± 7.44)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	14.1 (± 28.13)	2.8 (± 9.42)		
Double Blind Week 40- Tapering Arm (n=11;61)	-2.3 (± 14.86)	1.1 (± 11.61)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	28.1 (± 39.77)	2.8 (± 9.42)		
Flare Week 0- Tapering Arm (n=28;0)	-5.1 (± 15.96)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=7;0)	2.7 (± 7.09)	999 (± 999)		

Flare Week 4- Tapering Arm (n=25;0)	-5.0 (± 19.52)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=6;0)	3.1 (± 7.65)	999 (± 999)		
Flare Week 10- Tapering Arm (n=27;0)	-3.7 (± 13.90)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	2.7 (± 7.09)	999 (± 999)		
Flare Week 16- Tapering Arm (n=28;0)	-2.0 (± 6.60)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	2.7 (± 7.09)	999 (± 999)		

Notes:

[63] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[64] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Convenience Score

End point title	Mean Change From Double-blind Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Convenience Score

End point description:

Participants completed the 14-item Treatment Satisfaction Questionnaire for Medication (TSQM; Version 1.4) to assess satisfaction with their current rheumatoid arthritis treatment over the previous 2-3 weeks or since the last time that they took the medication. The TSQM consists of fourteen items over four domains (effectiveness, side effects, convenience, and global satisfaction). The 14 questions are answered either with yes/no or by means of a five or seven stage scale (ranging from very unsatisfied to satisfied). TSQM Scale scores for each domain range from 0 to 100 and higher scores represent higher satisfaction. Negative values indicate worsening from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

At Weeks 4, 16, 28, and 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[65]	74[66]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 16- Tapering Arm (n=35;61)	-0.2 (± 16.96)	0.8 (± 13.45)		
Double Blind Week 16- Withdrawal Arm (n=8;11)	-4.9 (± 19.57)	4.0 (± 10.86)		
Double Blind Week 28- Tapering Arm (n=16;61)	0.0 (± 18.70)	-1.0 (± 15.47)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	-4.2 (± 12.32)	-3.5 (± 13.21)		
Double Blind Week 40- Tapering Arm (n=11;61)	-4.0 (± 9.65)	-0.1 (± 16.50)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	-16.7 (± 23.57)	2.5 (± 18.32)		
Flare Week 0- Tapering Arm (n=28;0)	4.2 (± 12.53)	999 (± 999)		

Flare Week 0- Withdrawal Arm (n=7;0)	-7.1 (± 14.60)	999 (± 999)		
Flare Week 4- Tapering Arm (n=25;0)	4.4 (± 19.84)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=6;0)	5.6 (± 18.92)	999 (± 999)		
Flare Week 10- Tapering Arm (n=27;0)	1.2 (± 10.60)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	0.8 (± 16.49)	999 (± 999)		
Flare Week 16- Tapering Arm (n=28;0)	1.6 (± 19.65)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	0.8 (± 20.89)	999 (± 999)		

Notes:

[65] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[66] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Global Satisfaction Score

End point title	Mean Change From Double-blind Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Global Satisfaction Score

End point description:

Participants completed the 14-item Treatment Satisfaction Questionnaire for Medication (TSQM; Version 1.4) to assess satisfaction with their current rheumatoid arthritis treatment over the previous 2-3 weeks or since the last time that they took the medication. The TSQM consists of fourteen items over four domains (effectiveness, side effects, convenience, and global satisfaction). The 14 questions are answered either with yes/no or by means of a five or seven stage scale (ranging from very unsatisfied to satisfied). TSQM Scale scores for each domain range from 0 to 100 and higher scores represent higher satisfaction. Negative values indicate worsening from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

At Weeks 4, 16, 28, and 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[67]	74[68]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 16- Tapering Arm (n=35;61)	-11.6 (± 24.99)	-3.4 (± 17.91)		
Double Blind Week 16- Withdrawal Arm (n=8;11)	-2.7 (± 15.24)	0.6 (± 22.69)		
Double Blind Week 28- Tapering Arm (n=16;61)	-2.2 (± 12.70)	-5.7 (± 14.97)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	5.4 (± 15.84)	-4.5 (± 25.81)		
Double Blind Week 40- Tapering Arm (n=11;61)	-3.2 (± 13.31)	-2.6 (± 15.10)		

Double Blind Week 40- Withdrawal Arm (n=2;11)	0.0 (± 10.10)	-3.2 (± 21.98)		
Flare Week 0- Tapering Arm (n=28;0)	-11.7 (± 27.58)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=7;0)	-9.2 (± 25.66)	999 (± 999)		
Flare Week 4- Tapering Arm (n=25;0)	-3.1 (± 20.32)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=6;0)	-1.2 (± 24.08)	999 (± 999)		
Flare Week 10- Tapering Arm (n=27;0)	-0.8 (± 13.77)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	-2.0 (± 18.77)	999 (± 999)		
Flare Week 16- Tapering Arm (n=28;0)	-6.6 (± 24.20)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	-8.2 (± 16.72)	999 (± 999)		

Notes:

[67] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[68] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Work Productivity and Activity Impairment (WPAI) Overall Work Impairment and Activity Impairment Scores

End point title	Mean Change From Double-blind Baseline in Work Productivity and Activity Impairment (WPAI) Overall Work Impairment and Activity Impairment Scores

End point description:

The Work Productivity and Activity Impairment (WPAI) questionnaire for general health is a validated tool in rheumatoid arthritis consisting of 6 questions, based on participant recall of the previous 7 days. WPAI assesses work time missed due to illness (absenteeism), impairment at work due to health (presenteeism), overall work impairment due to health (an aggregate measure of both absenteeism and presenteeism), and total non-occupational activity impairment due to health. WPAI scores are expressed as impairment percentages, with higher scores indicating worse outcomes. A negative change from baseline indicates improvement. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= 0 participants for this time point; 9999= not calculable/estimable due to an insufficient number of subjects with an observation

End point type	Secondary

End point timeframe:

At Weeks 4, 28, and 40 and Flare Weeks 0, 10, and 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[69]	75[70]		
Units: percent impairment				
arithmetic mean (standard deviation)				
Overall Work Impairment Wk 28- Tapering (n=2;27)	15.0 (± 21.21)	3.5 (± 10.68)		
Overall Work Impairment Wk 28- Withdrawal (n=1;5)	0.0 (± 9999)	0.6 (± 8.12)		
Activity Impairment Wk 28- Tapering (n=14;61)	5.0 (± 19.51)	2.8 (± 13.43)		

Activity Impairment Wk 28- Withdrawal (n=3;11)	10.0 (± 17.32)	-0.9 (± 7.01)		
Overall Work Impairment Wk 40- Tapering (n=0;28)	999 (± 999)	3.4 (± 18.78)		
Overall Work Impairment Wk 40- Withdrawal (n=0;5)	999 (± 999)	0.6 (± 8.12)		
Activity Impairment Wk 40- Tapering (n=7;61)	15.7 (± 9.76)	0.5 (± 13.59)		
Activity Impairment Wk 40- Withdrawal (n=1;11)	20.0 (± 9999)	0.0 (± 6.32)		
Overall Work Impairment Flare 0- Tapering (5;0)	14.0 (± 27.02)	999 (± 999)		
Overall Work Impairment Flare 0- Withdrawal (n=2;0)	5.0 (± 7.07)	999 (± 999)		
Activity Impairment Flare Wk 0- Tapering (n=22;0)	25.9 (± 31.57)	999 (± 999)		
Activity Impairment Flare Wk 0- Withdrawal (n=5;0)	8.0 (± 25.88)	999 (± 999)		
Overall Work Impairment Flare 10- Tapering (n=8;0)	-0.2 (± 8.78)	999 (± 999)		
Overall Work Impairment Flare 10- Withdrawal (n=2;0	5.0 (± 7.07)	999 (± 999)		
Activity Impairment Flare Wk 10- Tapering (n=26;0)	6.5 (± 15.48)	999 (± 999)		
Activity Impairment Flare Wk 10- Withdrawal (n=7;0)	12.9 (± 13.80)	999 (± 999)		
Overall Work Impairment Flare 16- Tapering (n=8;0)	10.0 (± 14.82)	999 (± 999)		
Overall Work Impairment Flare 16- Withdrawal (n=3;0	10.0 (± 10.00)	999 (± 999)		
Activity Impairment Flare Wk 16- Tapering (n=29;0)	11.0 (± 17.39)	999 (± 999)		
Activity Impairment Flare Wk 16- Withdrawal (n=8;0)	8.8 (± 11.26)	999 (± 999)		

Notes:

[69] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[70] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Short-Form 36 Version 2 Health Survey (SF-36v2) Physical Component Summary (PCS) Score

End point title	Mean Change From Double-blind Baseline in Short-Form 36 Version 2 Health Survey (SF-36v2) Physical Component Summary (PCS) Score

End point description:

The SF-36v2 is a non-disease specific Health Related Quality of Life (HRQoL) instrument. The SF-36v2 comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) with a recall period of four weeks. Domain scores are aggregated into a Physical Component Summary (PCS) score and a Mental Component Summary (MCS) score. SF-36v2 scores for each domain and PCS/MCS range from 0-100: higher scores indicate a better state of health and a decrease from baseline represents worsening. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data; 9999= not calculable/estimable due to an insufficient number of subjects with an observation

End point type	Secondary

End point timeframe:

At Weeks 4, 28, and 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45[71]	74[72]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 28- Tapering Arm (n=13;60)	-2.9 (± 7.53)	-1.1 (± 4.18)		
Double Blind Week 28- Withdrawal Arm (n=3;11)	-1.9 (± 7.39)	-2.4 (± 3.97)		
Double Blind Week 40- Tapering Arm (n=6;60)	-5.5 (± 6.42)	-0.4 (± 5.53)		
Double Blind Week 40- Withdrawal Arm (n=1;11)	-1.6 (± 9999)	-2.1 (± 5.22)		
Flare Week 0- Tapering Arm (n=22;0)	-10.8 (± 10.85)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=5;0)	-2.4 (± 10.81)	999 (± 999)		
Flare Week 4- Tapering Arm (n=24;0)	-5.2 (± 8.37)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=6;0)	-8.0 (± 7.35)	999 (± 999)		
Flare Week 10- Tapering Arm (n=25;0)	-4.0 (± 7.22)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	-4.0 (± 4.57)	999 (± 999)		
Flare Week 16- Tapering Arm (n=28;0)	-3.8 (± 7.38)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	-2.5 (± 2.80)	999 (± 999)		

Notes:

[71] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[72] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Short-Form 36 Version 2 Health Survey (SF-36v2) Mental Component Summary (MCS) Score

End point title	Mean Change From Double-blind Baseline in Short-Form 36 Version 2 Health Survey (SF-36v2) Mental Component Summary (MCS) Score

End point description:

The SF-36v2 is a non-disease specific Health Related Quality of Life (HRQoL) instrument. The SF-36v2 comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) with a recall period of four weeks. Domain scores are aggregated into a Physical Component Summary (PCS) score and a Mental Component Summary (MCS) score. SF-36v2 scores for each domain and PCS/MCS range from 0-100: higher scores indicate a better state of health and a decrease from baseline represents worsening. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data; 9999= not calculable/estimable due to an insufficient number of subjects with an observation

End point type	Secondary

End point timeframe:

At Weeks 4, 28, and 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45[73]	74[74]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 28- Tapering Arm (n=13;60)	-5.5 (± 11.31)	-0.8 (± 6.02)		
Double Blind Week 28- Withdrawal Arm (n=3;11)	-5.2 (± 5.90)	-0.1 (± 7.20)		
Double Blind Week 40- Tapering Arm (n=6;60)	-3.5 (± 11.14)	-0.8 (± 5.89)		
Double Blind Week 40- Withdrawal Arm (n=1;11)	-8.5 (± 9999)	-0.4 (± 6.71)		
Flare Week 0- Tapering Arm (n=22;0)	-4.1 (± 11.43)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=5;0)	0.4 (± 4.59)	999 (± 999)		
Flare Week 4- Tapering Arm (n=24;0)	-2.0 (± 5.95)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=6;0)	-0.5 (± 2.51)	999 (± 999)		
Flare Week 10- Tapering Arm (n=25;0)	-1.1 (± 10.14)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	-0.4 (± 3.06)	999 (± 999)		
Flare Week 16- Tapering Arm (n=28;0)	-4.0 (± 11.01)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	0.1 (± 2.55)	999 (± 999)		

Notes:

[73] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[74] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

End point title	Mean Change From Double-blind Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

End point description:

The FACIT-Fatigue questionnaire is a participant questionnaire that consists of 13 questions designed to measure the degree of fatigue experienced by participants in the previous 7 days. Participants respond to the questions on a scale from 'not at all' (0) to 'very much' (4). The scale score is computed by summing the item scores, after reversing those items that are worded in the negative direction. The FACIT-Fatigue subscale score ranges from 0 to 52, where higher scores represent less fatigue. A negative change from baseline indicates worsening. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

At Weeks 4, 16, 28, and 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[75]	74[76]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Double Blind Week 16- Tapering Arm (n=35;61)	-6.0 (± 9.80)	-1.5 (± 5.42)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	-2.3 (± 3.39)	-1.9 (± 3.27)		
Double Blind Week 28- Tapering Arm (n=16;61)	-3.5 (± 7.58)	-1.6 (± 5.60)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	-4.3 (± 7.23)	-2.2 (± 4.67)		
Double Blind Week 40- Tapering Arm (n=11;61)	-6.4 (± 8.44)	-0.4 (± 4.00)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	-2.5 (± 6.36)	-1.5 (± 4.78)		
Flare Week 0- Tapering Arm (n=28;0)	-7.4 (± 11.17)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	-3.6 (± 4.75)	999 (± 999)		
Flare Week 4- Tapering Arm (n=25;0)	-3.8 (± 9.19)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=6;0)	-4.7 (± 5.43)	999 (± 999)		
Flare Week 10- Tapering Arm (n=27;0)	-3.9 (± 8.44)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=7;0)	-2.4 (± 4.47)	999 (± 999)		
Flare Week 16- Tapering Arm (n=28;0)	-4.5 (± 9.01)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=7;0)	-1.7 (± 1.89)	999 (± 999)		

Notes:

[75] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[76] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Serum Levels of C-reactive Protein (CRP)

End point title	Mean Change From Double-blind Baseline in Serum Levels of C-reactive Protein (CRP)

End point description:

C-Reactive Protein (CRP; mg/L) was measured from blood samples as a marker for inflammation. Higher levels are indicative of more inflammation. Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[77]	76[78]		
Units: mg/L				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=36;64)	-7.9 (± 48.87)	1.7 (± 12.92)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	-0.2 (± 3.55)	-0.6 (± 2.53)		
Double Blind Week 16- Tapering Arm (n=35;63)	-7.4 (± 49.77)	-0.4 (± 4.26)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	6.6 (± 12.26)	-0.1 (± 3.67)		
Double Blind Week 22- Tapering Arm (n=19;63)	3.6 (± 9.69)	-0.0 (± 5.43)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	0.6 (± 0.37)	-0.9 (± 3.38)		
Double Blind Week 28- Tapering Arm (n=16;63)	0.5 (± 3.85)	-0.4 (± 4.65)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	1.1 (± 1.34)	2.5 (± 11.60)		
Double Blind Week 34- Tapering Arm (n=12;63)	3.2 (± 10.13)	-0.4 (± 4.41)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	1.8 (± 1.89)	0.3 (± 5.98)		
Double Blind Week 40- Tapering Arm (n=11;63)	1.0 (± 5.69)	-0.3 (± 4.18)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	8.3 (± 11.60)	-0.1 (± 3.43)		
Flare Week 0- Tapering Arm (n=30;0)	-7.4 (± 54.12)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	5.4 (± 12.67)	999 (± 999)		
Flare Week 4- Tapering Arm (n=30;0)	-8.5 (± 55.47)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=8;0)	-1.3 (± 4.01)	999 (± 999)		
Flare Week 10- Tapering Arm (n=30;0)	-9.5 (± 55.61)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=8;0)	-0.6 (± 0.97)	999 (± 999)		
Flare Week 16- Tapering Arm (n=30;0)	-9.1 (± 53.70)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	-0.8 (± 2.74)	999 (± 999)		

Notes:

[77] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[78] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Double-blind Baseline in Serum Levels of Erythrocyte Sedimentation Rate (ESR)

End point title	Mean Change From Double-blind Baseline in Serum Levels of Erythrocyte Sedimentation Rate (ESR)

End point description:

Erythrocyte sedimentation rate (ESR; mm/hour) indirectly measures how much inflammation is in the

body. A higher ESR is indicative of increased inflammation. Negative values indicate improvement from baseline. For Double-blind period data, missing values were only imputed up to the time when the participant entered the Open-label rescue period. 999= subjects did not experience flare and do not have Flare Week data

End point type	Secondary

End point timeframe:

From Week 4 to Week 40 and from Flare Week 0 to Flare Week 16

End point values	Flared Participants	Non-Flared Participants		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[79]	76[80]		
Units: mm/hour				
arithmetic mean (standard deviation)				
Double Blind Week 10- Tapering Arm (n=37;64)	4.1 (± 11.25)	0.7 (± 5.22)		
Double Blind Week 10- Withdrawal Arm (n=9;11)	0.9 (± 9.24)	-1.5 (± 5.43)		
Double Blind Week 16- Tapering Arm (n=35;63)	4.6 (± 10.73)	0.5 (± 5.82)		
Double Blind Week 16- Withdrawal Arm (n=9;11)	5.2 (± 15.23)	-0.3 (± 5.31)		
Double Blind Week 22- Tapering Arm (n=19;63)	3.5 (± 10.73)	-0.5 (± 7.38)		
Double Blind Week 22- Withdrawal Arm (n=4;11)	2.8 (± 9.22)	-0.3 (± 4.22)		
Double Blind Week 28- Tapering Arm (n=16;63)	3.4 (± 8.18)	0.4 (± 6.93)		
Double Blind Week 28- Withdrawal Arm (n=4;11)	6.0 (± 10.10)	1.0 (± 5.04)		
Double Blind Week 34- Tapering Arm (n=12;63)	4.8 (± 7.28)	0.3 (± 7.57)		
Double Blind Week 34- Withdrawal Arm (n=2;11)	-5.0 (± 1.41)	-0.5 (± 5.94)		
Double Blind Week 40- Tapering Arm (n=11;63)	10.2 (± 13.22)	1.4 (± 7.19)		
Double Blind Week 40- Withdrawal Arm (n=2;11)	-2.0 (± 5.66)	4.7 (± 8.89)		
Flare Week 0- Tapering Arm (n=30;0)	10.4 (± 12.50)	999 (± 999)		
Flare Week 0- Withdrawal Arm (n=8;0)	13.0 (± 11.90)	999 (± 999)		
Flare Week 4- Tapering Arm (n=30;0)	7.2 (± 9.82)	999 (± 999)		
Flare Week 4- Withdrawal Arm (n=8;0)	8.5 (± 9.52)	999 (± 999)		
Flare Week 10- Tapering Arm (n=30;0)	5.8 (± 10.16)	999 (± 999)		
Flare Week 10- Withdrawal Arm (n=8;0)	4.4 (± 6.91)	999 (± 999)		
Flare Week 16- Tapering Arm (n=30;0)	8.0 (± 10.95)	999 (± 999)		
Flare Week 16- Withdrawal Arm (n=8;0)	7.0 (± 14.40)	999 (± 999)		

Notes:

[79] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

[80] - Subjects rcvd ≥ 1 dose of study drug during Double-blind period (DB) & had at least DB Baseline data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) reported from time of study drug administration until 70 d after last dose (up to 50 wks for Double-blind); up to 66 wks for subjects who experienced flare during Double-blind

Adverse event reporting additional description:

TEAEs and TESAEs are defined as any adverse event (AE) with an onset date that is on or after the first dose of study drug until 70 days after the last dose of study drug and were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Adalimumab 40 mg Eow

Reporting group description:

40 mg adalimumab administered subcutaneously every other week (eow) from Week 0 to Week 4

Reporting group title	Adalimumab Withdrawal Arm

Reporting group description:

Placebo administered subcutaneously every three weeks from Week 4 to Week 40 (Double-blind Period)

Reporting group title	Adalimumab 40 mg Eow Rescue Arm

Reporting group description:

40 mg adalimumab administered subcutaneously every other week from Flare Week 0 to Flare Week 16 (Open-label Rescue Period)

Reporting group title	Adalimumab Tapering

Reporting group description:

40 mg adalimumab administered subcutaneously every three weeks from Week 4 to Week 40 (Double-blind Period)

Serious adverse events	Adalimumab 40 mg Eow	Adalimumab Withdrawal Arm	Adalimumab 40 mg Eow Rescue Arm
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 146 (2.74%)	0 / 20 (0.00%)	3 / 39 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER			
subjects affected / exposed	0 / 146 (0.00%)	0 / 20 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

COMMINUTED FRACTURE			
subjects affected / exposed	1 / 146 (0.68%)	0 / 20 (0.00%)	0 / 39 (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
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 146 (0.68%)	0 / 20 (0.00%)	0 / 39 (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
Nervous system disorders			
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 146 (0.68%)	0 / 20 (0.00%)	0 / 39 (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
Eye disorders			
RETINAL VEIN OCCLUSION			
subjects affected / exposed	0 / 146 (0.00%)	0 / 20 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			
subjects affected / exposed	0 / 146 (0.00%)	0 / 20 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
OSTEOARTHRITIS			
subjects affected / exposed	0 / 146 (0.00%)	0 / 20 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	1 / 146 (0.68%)	0 / 20 (0.00%)	0 / 39 (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

Serious adverse events	Adalimumab Tapering		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 102 (0.98%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
COMMINUTED FRACTURE			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
RETINAL VEIN OCCLUSION			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
OSTEOARTHRITIS			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Adalimumab 40 mg Eow	Adalimumab Withdrawal Arm	Adalimumab 40 mg Eow Rescue Arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 146 (7.53%)	12 / 20 (60.00%)	13 / 39 (33.33%)
Investigations			
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 146 (0.00%)	0 / 20 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
LIMB INJURY			
subjects affected / exposed	0 / 146 (0.00%)	2 / 20 (10.00%)	1 / 39 (2.56%)
occurrences (all)	0	2	1
MUSCLE STRAIN			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	1 / 39 (2.56%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			

COUGH			
subjects affected / exposed	4 / 146 (2.74%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	4	1	0
Renal and urinary disorders			
URINARY RETENTION			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 146 (0.00%)	0 / 20 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	0	1
BACK PAIN			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
MUSCULOSKELETAL STIFFNESS			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
NECK PAIN			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
OSTEOPOROSIS			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
INFLUENZA			
subjects affected / exposed	0 / 146 (0.00%)	2 / 20 (10.00%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 146 (0.68%)	1 / 20 (5.00%)	1 / 39 (2.56%)
occurrences (all)	1	1	1

NASOPHARYNGITIS			
subjects affected / exposed	4 / 146 (2.74%)	4 / 20 (20.00%)	4 / 39 (10.26%)
occurrences (all)	4	5	4
PHARYNGOTONSILLITIS			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
TONSILLITIS			
subjects affected / exposed	0 / 146 (0.00%)	1 / 20 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	1	0
TOOTH INFECTION			
subjects affected / exposed	1 / 146 (0.68%)	1 / 20 (5.00%)	1 / 39 (2.56%)
occurrences (all)	1	1	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 146 (0.00%)	0 / 20 (0.00%)	3 / 39 (7.69%)
occurrences (all)	0	0	3
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 146 (1.37%)	0 / 20 (0.00%)	2 / 39 (5.13%)
occurrences (all)	2	0	2

Non-serious adverse events	Adalimumab Tapering		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 102 (32.35%)		
Investigations			
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
LIMB INJURY			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
MUSCLE STRAIN			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		

General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	4 / 102 (3.92%)		
occurrences (all)	4		
Renal and urinary disorders			
URINARY RETENTION			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	10		
BACK PAIN			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
MUSCULOSKELETAL STIFFNESS			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
NECK PAIN			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
OSTEOPOROSIS			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
RHEUMATOID ARTHRITIS			
subjects affected / exposed	5 / 102 (4.90%)		
occurrences (all)	5		
Infections and infestations			

INFLUENZA			
subjects affected / exposed	5 / 102 (4.90%)		
occurrences (all)	6		
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	3		
NASOPHARYNGITIS			
subjects affected / exposed	16 / 102 (15.69%)		
occurrences (all)	17		
PHARYNGOTONSILLITIS			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
TONSILLITIS			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
TOOTH INFECTION			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2016	• Reduced sample size from 334 to ~200 • Allowed for 3 variables of the DAS28 (CRP or ESR) to satisfy inclusion criteria of patients in stable remission • Added that 3 variable DAS28 (ESR) score can be used for evaluation of flare when the physician's global assessment score not available • Changed time for required stable medications to ensure medication that affects risk of flare is stable • Clarified that once the limit of 20% of enrolled subjects on other csDMARDs or no csDMARDs is met, only subjects on concomitant MTX allowed into trial • Clarified language regarding MRI scans: scan dominant hand if both hands/wrists are affected • Clarified concomitant therapies (e.g. intra-muscular MTX, equivalent opioids to Tramadol, dose decrease related to MTX or other csDMARDs, folic acid dosage) • Removed azathioprine from exclusion criteria to allow for subjects previously treated • Clarified allowed dose interruption of adalimumab prior to the study • Clarified importance of stopping commercial adalimumab at enrollment • Ensured subject safety (e.g. MRI report for non-RA findings, csDMARD use while on rescue therapy, 70-day follow-up for AEs) • Increased number of sites and countries planned • Extended Screening and Lead-In time to ensure enough time for procedures, increased dosing window during the DB period, added option for shortened Early Termination Visit • Provided clarification re: urine pregnancy testing/timing, CDAI and SDAI calculation as part of statistical analysis, ESR testing, and tuberculosis (TB) screening; updated 24-hour medical surveillance contact information; added information regarding electronic PROs • Updated Complaint and Product Complaint definition and reporting requirements • Revised injection instructions to correct error regarding how many syringes the subject will take home • Revised timing of first dose of OL Rescue arm • Revised language regarding duration of treatment • Removed TB language re: Czech Republic

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported