# EU Clinical Trials Register

## 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 | 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 |
| 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 |
| 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 |
|     Other, not specified | 22 |
|     Adverse event, non-fatal | 2 |
|     Consent withdrawn by subject | 12 |

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 |
|     Other, not specified | 4 | 1 |
|     Adverse event, non-fatal | 1 | - |
|     Consent withdrawn by subject | 4 | - |

**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 |
|    Incorrectly entered Open-Label Rescue Period | 1 | - |
|    Consent withdrawn by subject | 2 | - |

## 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 | 59.6 | | |
|     standard deviation | ± 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 | 12.9 | | |
|     standard deviation | ± 9.99 | - | |

| Duration of adalimumab therapy | | | |
|---|---|---|---|
| Units: years | | | |
| arithmetic mean | 5.4 | | |
| standard deviation | ± 3.27 | - | |
| Duration of remission | | | |
| Participants with available data, n=125 | | | |
| Units: years | | | |
| arithmetic mean | 2.2 | | |
| standard deviation | ± 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 | 8.7 | | |
| standard deviation | ± 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 | 2.4 | | |
| standard deviation | ± 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 | 0.4 | | |
| standard deviation | ± 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

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## 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

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## 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) | | |

| End point values | | | | |
|---|---|---|---|---|
| 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:

| 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 |
| **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 |
| **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 |
| 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 |
| 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 |
| 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 |
| 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 | | |
| 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 | | |
| 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 | | |
| 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 | | |
| 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 | | |
| 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 | | |

| 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%) |
| 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 |
| 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 |
| 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 |

| | | | |
|---|---|---|---|
| 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 |
| 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 |
| OSTEOPOROSIS | | | |
| 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 |
| 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 | | | |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 1 / 20 (5.00%) | 1 / 39 (2.56%) |
| occurrences (all) | 1 | 1 | 1 |
| INFLUENZA | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 2 / 20 (10.00%) | 0 / 39 (0.00%) |

| | | | |
|---|---|---|---|
| occurrences (all) | 0 | 2 | 0 |
| 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 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 20 (0.00%) | 3 / 39 (7.69%) |
| occurrences (all) | 0 | 0 | 3 |
| TOOTH INFECTION | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 1 / 20 (5.00%) | 1 / 39 (2.56%) |
| occurrences (all) | 1 | 1 | 1 |
| 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%) | | |
| 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 | | |
| 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 | | | |

| | | | | |
|---|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| COUGH | | | | |
| subjects affected / exposed | 4 / 102 (3.92%) | | | |
| occurrences (all) | 4 | | | |
| **General disorders and administration site conditions** | | | | |
| OEDEMA PERIPHERAL | | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| **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 | | | |
| OSTEOPOROSIS | | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | | | |
| occurrences (all) | 0 | | | |
| NECK PAIN | | | | |
| 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 | | | |
|---|---|---|---|
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 102 (2.94%) | | |
| occurrences (all) | 3 | | |
| INFLUENZA | | | |
| subjects affected / exposed | 5 / 102 (4.90%) | | |
| occurrences (all) | 6 | | |
| 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 | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 102 (0.98%) | | |
| occurrences (all) | 1 | | |
| TOOTH INFECTION | | | |
| subjects affected / exposed | 0 / 102 (0.00%) | | |
| occurrences (all) | 0 | | |
| 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<br>• Allowed for 3 variables of the DAS28 (CRP or ESR) to satisfy inclusion criteria of patients in stable remission<br>• Added that 3 variable DAS28 (ESR) score can be used for evaluation of flare when the physician's global assessment score not available<br>• Changed time for required stable medications to ensure medication that affects risk of flare is stable<br>• 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<br>• Clarified language regarding MRI scans: scan dominant hand if both hands/wrists are affected<br>• Clarified concomitant therapies (e.g. intra-muscular MTX, equivalent opioids to Tramadol, dose decrease related to MTX or other csDMARDs, folic acid dosage)<br>• Removed azathioprine from exclusion criteria to allow for subjects previously treated<br>• Clarified allowed dose interruption of adalimumab prior to the study<br>• Clarified importance of stopping commercial adalimumab at enrollment<br>• Ensured subject safety (e.g. MRI report for non-RA findings, csDMARD use while on rescue therapy, 70-day follow-up for AEs)<br>• Increased number of sites and countries planned<br>• 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<br>• 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<br>• Updated Complaint and Product Complaint definition and reporting requirements<br>• Revised injection instructions to correct error regarding how many syringes the subject will take home<br>• Revised timing of first dose of OL Rescue arm<br>• Revised language regarding duration of treatment<br>• Removed TB language re: Czech Republic |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial?  No

### Limitations and caveats

 None reported