



Clinical trial results:

A multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Certolizumab Pegol in combination with Methotrexate for inducing and sustaining clinical response in the treatment of DMARD-Naïve adults with early active Rheumatoid Arthritis (c-early)

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2011-001729-25 |
| Trial protocol | BE DE IE HU ES CZ AT SE NL IT GB |
| Global end of trial date | |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 10 February 2016 |
| First version publication date | 24 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | RA0055 Period 1 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01519791 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB Pharma SA |
| Sponsor organisation address | Allée de la Recherche 60, Brussels, Belgium, B-1070 |
| Public contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 4815 15, clinicaltrials@ucb.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.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 | Interim |
| Date of interim/final analysis | 03 October 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 July 2014 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate that the combination of CZP + MTX is superior to PBO + MTX in achieving sustained remission by Week 52.

Protection of trial subjects:

Not applicable

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 25 January 2012 |
| 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 | Argentina: 35 |
| Country: Number of subjects enrolled | Australia: 37 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Belgium: 25 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | Colombia: 29 |
| Country: Number of subjects enrolled | Czech Republic: 39 |
| Country: Number of subjects enrolled | France: 12 |
| Country: Number of subjects enrolled | Germany: 86 |
| Country: Number of subjects enrolled | Hungary: 42 |
| Country: Number of subjects enrolled | Ireland: 7 |
| Country: Number of subjects enrolled | Italy: 13 |
| Country: Number of subjects enrolled | Mexico: 42 |
| Country: Number of subjects enrolled | Netherlands: 8 |
| Country: Number of subjects enrolled | Poland: 118 |
| Country: Number of subjects enrolled | Romania: 16 |
| Country: Number of subjects enrolled | Spain: 16 |
| Country: Number of subjects enrolled | Sweden: 15 |
| Country: Number of subjects enrolled | Switzerland: 6 |
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Country: Number of subjects enrolled | United States: 302 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 879 |
| EEA total number of subjects | 423 |

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) | 745 |
| From 65 to 84 years | 133 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in January 2012.

Pre-assignment

Screening details:

A total of 880 subjects were randomized. Three subjects were randomized in error, were not dosed, and withdrawn shortly afterwards as screen failures. Two of them were included in the Randomized Set 1 (RS1) only and one of these three subjects was conservatively excluded from any output. Therefore, 879 subjects are in RS1.

Period 1

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

Arms

| | |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo + Methotrexate |

Arm description:

Placebo + Methotrexate (MTX) 2 syringes Placebo at Baseline, Week 2 and Week 4 + MTX, followed by 1 syringe Placebo every 2 Weeks + MTX. The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

| | |
|--|--------------|
| Arm type | Placebo |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | MTX |
| Other name | Trexan |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The MTX treatment is to be initiated at a dose of 10 mg per Week (oral tablets at the strength of 2.5 mg/tablet). The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8. Patients who could not tolerate ≥ 15 mg/week MTX by Week 8 were withdrawn while the maximum tolerated dose per patient (optimized dose) was maintained to Week 52.

| | |
|------------------|-----------------------------------|
| Arm title | Certolizumab Pegol + Methotrexate |
|------------------|-----------------------------------|

Arm description:

Certolizumab Pegol + Methotrexate (MTX) Prefilled syringes containing an injectable volume of 1 ml of solution for injection CZP for single use at a dosage strength of 200 mg/ml. Injections will be given subcutaneously. CZP 400 mg + MTX at Baseline, Week 2 and Week 4, followed by a maintenance dose of CZP 200 mg + MTX every 2 Weeks until Week 50. The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Certolizumab pegol |
| Investigational medicinal product code | CDP870 |
| Other name | Cimzia |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subcutaneous injections: CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose

of 200 mg every 2 Weeks until Week 50.

| | |
|--|--------------|
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | MTX |
| Other name | Trexan |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The MTX treatment is to be initiated at a dose of 10 mg per Week (oral tablets at the strength of 2.5 mg/tablet). The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8. Patients who could not tolerate ≥ 15 mg/week MTX by Week 8 were withdrawn while the maximum tolerated dose per patient (optimized dose) was maintained to Week 52.

| Number of subjects in period 1 | Placebo + Methotrexate | Certolizumab Pegol + Methotrexate |
|--|-----------------------------------|--|
| Started | 219 | 660 |
| Completed Week 52 | 143 | 500 |
| Completed | 67 | 292 |
| Not completed | 152 | 368 |
| AE, serious fatal | - | 1 |
| Consent withdrawn by subject | 15 | 37 |
| SAE, fatal + SAE, non-fatal | - | 1 |
| AE, non-serious non-fatal | 12 | 31 |
| Other Reason | 87 | 222 |
| 'subjects randomized in error ' | 2 | - |
| Lost to follow-up | 6 | 14 |
| SAE, non-fatal | 6 | 22 |
| Lack of efficacy | 16 | 20 |
| Protocol deviation | 6 | 19 |
| SAE, non-fatal + AE, non-serious non-fatal | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Methotrexate |
|-----------------------|------------------------|

Reporting group description:

Placebo + Methotrexate (MTX) 2 syringes Placebo at Baseline, Week 2 and Week 4 + MTX, followed by 1 syringe Placebo every 2 Weeks + MTX. The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Certolizumab Pegol + Methotrexate |
|-----------------------|-----------------------------------|

Reporting group description:

Certolizumab Pegol + Methotrexate (MTX) Prefilled syringes containing an injectable volume of 1 ml of solution for injection CZP for single use at a dosage strength of 200 mg/ml. Injections will be given subcutaneously. CZP 400 mg + MTX at Baseline, Week 2 and Week 4, followed by a maintenance dose of CZP 200 mg + MTX every 2 Weeks until Week 50. The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

| Reporting group values | Placebo + Methotrexate | Certolizumab Pegol + Methotrexate | Total |
|------------------------|---------------------------|--------------------------------------|-------|
| Number of subjects | 219 | 660 | 879 |
| Age categorical | | | |
| Units: Subjects | | | |
| <=18 | 1 | 2 | 3 |
| >18-<65 | 182 | 560 | 742 |
| >=65 | 36 | 98 | 134 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 51.3 | 50.5 | |
| standard deviation | ± 13.2 | ± 13.6 | - |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Male | 44 | 161 | 205 |
| Female | 175 | 499 | 674 |

End points

End points reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Methotrexate |
|-----------------------|------------------------|

Reporting group description:

Placebo + Methotrexate (MTX) 2 syringes Placebo at Baseline, Week 2 and Week 4 + MTX, followed by 1 syringe Placebo every 2 Weeks + MTX. The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Certolizumab Pegol + Methotrexate |
|-----------------------|-----------------------------------|

Reporting group description:

Certolizumab Pegol + Methotrexate (MTX) Prefilled syringes containing an injectable volume of 1 ml of solution for injection CZP for single use at a dosage strength of 200 mg/ml. Injections will be given subcutaneously. CZP 400 mg + MTX at Baseline, Week 2 and Week 4, followed by a maintenance dose of CZP 200 mg + MTX every 2 Weeks until Week 50. The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

| | |
|----------------------------|--|
| Subject analysis set title | Placebo + Methotrexate (Full Analysis Set) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Placebo + Methotrexate (MTX)

2 syringes Placebo at Baseline, Week 2 and Week 4 + MTX, followed by 1 syringe Placebo every 2 Weeks + MTX.

The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

Full Analysis Set Period 1 (FAS1) consisted of all subjects with valid Baseline and valid post-Baseline efficacy measurement within Period 1 for DAS28(ESR).

| | |
|----------------------------|--|
| Subject analysis set title | Certolizumab Pegol + Methotrexate (Radiographic Set) |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Certolizumab Pegol + Methotrexate (MTX)

Prefilled syringes containing an injectable volume of 1 ml of solution for injection CZP for single use at a dosage strength of 200 mg/ml.

Injections will be given subcutaneously. CZP 400 mg + MTX at Baseline, Week 2 and Week 4, followed by a maintenance dose of CZP 200 mg + MTX every 2 Weeks until Week 50.

The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

The Radiographic Set Period 1 (RAD1) consisted of those subjects in the FAS1 who had provided valid radiographs (ie, radiographs resulting in a nonmissing mTSS score) at Baseline and at Week 52 or the Withdrawal Visit.

| | |
|----------------------------|---|
| Subject analysis set title | Placebo + Methotrexate (Radiographic Set) |
|----------------------------|---|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Placebo + Methotrexate (MTX)

2 syringes Placebo at Baseline, Week 2 and Week 4 + MTX, followed by 1 syringe Placebo every 2 Weeks + MTX.

The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

The Radiographic Set Period 1 (RAD1) consisted of those subjects in the FAS1 who had provided valid

radiographs (ie, radiographs resulting in a nonmissing mTSS score) at Baseline and at Week 52 or the Withdrawal Visit.

| | |
|----------------------------|---|
| Subject analysis set title | Certolizumab Pegol + Methotrexate (Full Analysis Set) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Certolizumab Pegol + Methotrexate (MTX)

Prefilled syringes containing an injectable volume of 1 ml of solution for injection CZP for single use at a dosage strength of 200 mg/ml.

Injections will be given subcutaneously. CZP 400 mg + MTX at Baseline, Week 2 and Week 4, followed by a maintenance dose of CZP 200 mg + MTX every 2 Weeks until Week 50.

The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

Full Analysis Set Period 1 (FAS1) consisted of all subjects with valid Baseline and valid post-Baseline efficacy measurement within Period 1 for DAS28(ESR).

Primary: Percentage of subjects in sustained remission at Week 52

| | |
|-----------------|--|
| End point title | Percentage of subjects in sustained remission at Week 52 |
|-----------------|--|

End point description:

Sustained remission is defined as a Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28[ESR]) < 2.6 at both Weeks 40 and 52.

DAS28[ESR] is calculated using the Tender Joint Count (TJC), Swollen Joint Count (SJC) Erythrocyte Sedimentation Rate (ESR in mm/hour), and the Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm) using the following formula:

$0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \log_{10}(ESR) + 0.014 \times PtGADA$,
where 28 joints are examined and a lower score indicates less disease activity.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 15 | 28.9 | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

In order to control the overall study-wise Type I error rate at 5 %, hypothesis testing was performed in the following hierarchical order (each at a 2-sided 95 % alpha level):

1. Primary: sustained DAS28(ESR) remission at Week 52
2. Key secondary: sustained DAS28(ESR) LDA at Week 52
3. ACR50 response at Week 52 in relation to Baseline

4. Change from Baseline in HAQ-DI at Week 52

5. Change from Baseline in mTSS at Week 52

| | |
|---|--|
| Comparison groups | Certolizumab Pegol + Methotrexate (Full Analysis Set) v Placebo + Methotrexate (Full Analysis Set) |
| Number of subjects included in analysis | 868 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[1] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.283 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.503 |
| upper limit | 3.468 |

Notes:

[1] - The Odds ratio measuring the treatment effect was estimated from a logistic regression model including terms for treatment, region and stratification factor. Nonresponder imputation (NRI) was used.

Secondary: Percentage of subjects in sustained Low Disease Activity (LDA) at Week 52

| | |
|---|---|
| End point title | Percentage of subjects in sustained Low Disease Activity (LDA) at Week 52 |
| End point description: | |
| Sustained LDA is defined as a Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28[ESR]) ≤ 3.2 at both Weeks 40 and 52. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 28.6 | 43.8 | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

In order to control the overall study-wise Type I error rate at 5 %, hypothesis testing was performed in the following hierarchical order (each at a 2-sided 95 % alpha level):

1. Primary: sustained DAS28(ESR) remission at Week 52
2. Key secondary: sustained DAS28(ESR) LDA at Week 52
3. ACR50 response at Week 52 in relation to Baseline

4. Change from Baseline in HAQ-DI at Week 52

5. Change from Baseline in mTSS at Week 52

| | |
|---|--|
| Comparison groups | Placebo + Methotrexate (Full Analysis Set) v Certolizumab Pegol + Methotrexate (Full Analysis Set) |
| Number of subjects included in analysis | 868 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[2] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.957 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.384 |
| upper limit | 2.767 |

Notes:

[2] - The Odds ratio measuring the treatment effect was estimated from a logistic regression model including terms for treatment, region and stratification factor. Nonresponder imputation (NRI) was used.

Secondary: Change from Baseline in modified Total Sharp Score (mTSS) to Week 52

| | |
|---|--|
| End point title | Change from Baseline in modified Total Sharp Score (mTSS) to Week 52 |
| End point description: Van der Heijde modified Total Sharp Score (mTSS) is a methodology to assess the degree of joint damage by quantifying the extent of bone erosions and joint space narrowing for 64 and 52 joints, respectively, with higher scores representing greater damage. | |
| End point type | Secondary |
| End point timeframe: From Baseline (Week 0) to Week 52 | |

| End point values | Placebo + Methotrexate (Radiographic Set) | Certolizumab Pegol + Methotrexate (Radiographic Set) | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 528 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 1.9 (± 4.8) | 0.2 (± 3.3) | | |

Statistical analyses

| | |
|--|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: In order to control the overall study-wise Type I error rate at 5 %, hypothesis testing was performed in the following hierarchical order (each at a 2-sided 95 % alpha level): 1. Primary: sustained DAS28(ESR) remission at Week 52 2. Key secondary: sustained DAS28(ESR) LDA at Week 52 3. ACR50 response at Week 52 in relation to Baseline | |

4. Change from Baseline in HAQ-DI at Week 52

5. Change from Baseline in mTSS at Week 52

| | |
|---|--|
| Comparison groups | Placebo + Methotrexate (Radiographic Set) v Certolizumab Pegol + Methotrexate (Radiographic Set) |
| Number of subjects included in analysis | 691 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[3] |
| Method | ANCOVA on ranks |
| Parameter estimate | Hodges-Lehmann point estimate of shift |
| Point estimate | 0.986 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.014 |

Notes:

[3] - ANCOVA model on the ranks with the terms for treatment, region, and time since RA diagnosis at Baseline (≤ 4 months or > 4 months) as factors and rank Baseline value as a covariate.

Confidence Interval is an asymptotic Moses CI.

Secondary: Percentage of subjects with radiographic non-progression from Baseline to Week 52

| | |
|--|---|
| End point title | Percentage of subjects with radiographic non-progression from Baseline to Week 52 |
| End point description: | |
| Radiographic non-progression is defined as change in mTSS ≤ 0.5 . | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline (Week 0) to Week 52 | |

| End point values | Placebo + Methotrexate (Radiographic Set) | Certolizumab Pegol + Methotrexate (Radiographic Set) | | |
|-------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 528 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 49.7 | 70.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the joint erosion score to Week 52

| | |
|-----------------|--|
| End point title | Change from Baseline in the joint erosion score to Week 52 |
|-----------------|--|

End point description:

Erosions were assessed in 16 locations per hand and 6 joints per foot. Erosions for each hand location were scored from 0 to 5, with 0 indicating no erosion. Scores 1 to 5 may have included combinations of discrete erosion(s) and/or large erosions. Erosions for each foot joint were scored from 0 to 10, with 0 indicating no erosions.

The maximum possible erosion score for all 32-hand joints was 160. The maximum possible erosion score for all 12 feet joints was 120. Thus, the maximum possible total erosion score for hands and feet was 280.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Week 0) to Week 52

| End point values | Placebo + Methotrexate (Radiographic Set) | Certolizumab Pegol + Methotrexate (Radiographic Set) | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 528 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 1.2 (± 3.7) | 0.1 (± 2.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Joint narrowing score to Week 52

| | |
|-----------------|--|
| End point title | Change from Baseline in the Joint narrowing score to Week 52 |
|-----------------|--|

End point description:

Joint space narrowing (JSN) was assessed in 15 locations per hand and 6 locations per foot. Joint space narrowing for each location was scored from 0 to 4, with 0 indicating no narrowing. The maximum possible score for JSN in all 30 hand joints was 120. The maximum possible score for JSN in all 12 feet joints was 48. Thus, the maximum possible total JSN score for Hands and feet was 168.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Week 0) to Week 52

| End point values | Placebo + Methotrexate (Radiographic Set) | Certolizumab Pegol + Methotrexate (Radiographic Set) | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 528 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 0.7 (± 2.3) | 0.1 (± 1.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects meeting the American College of Rheumatology 20 % response criteria (ACR20) at Week 52

| | |
|-----------------|---|
| End point title | Percentage of subjects meeting the American College of Rheumatology 20 % response criteria (ACR20) at Week 52 |
|-----------------|---|

End point description:

The assessments are based on a 20 % or greater improvement from Baseline in the number of tender joints, a 20 % or more improvement in the number of swollen joints, and a 20 % or greater improvement in 3 of the 5 remaining core set measures: Patient's Global Assessment of Disease Activity (PtGADA), Physician's Global Assessment of Disease Activity (PhGADA), Patient's Assessment of Arthritis Pain (PtAAP), physical function as assessed by the Health Assessment Questionnaire - Disability Index (HAQ-DI) and C-Reactive Protein (CRP).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Week 0) to Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 61.5 | 69 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects meeting the American College of Rheumatology 50 % response criteria (ACR50) at Week 52

| | |
|-----------------|---|
| End point title | Percentage of subjects meeting the American College of Rheumatology 50 % response criteria (ACR50) at Week 52 |
|-----------------|---|

End point description:

The assessments are based on a 50 % or greater improvement from Baseline in the number of tender joints, a 50 %, or more improvement in the number of swollen joints, and a 50 % or greater improvement in 3 of the 5 remaining core set measures: Patient's Global Assessment of Disease Activity (PtGADA), Physician's Global Assessment of Disease Activity (PhGADA), Patient's Assessment of Arthritis Pain (PtAAP), physical function as assessed by the Health Assessment Questionnaire - Disability Index (HAQ-DI) and C-Reactive Protein (CRP).

| | |
|-----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline (Week 0) to Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 52.6 | 61.8 | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|----------------------------|------------------------|

Statistical analysis description:

In order to control the overall study-wise Type I error rate at 5 %, hypothesis testing was performed in the following hierarchical order (each at a 2-sided 95 % alpha level):

1. Primary: sustained DAS28(ESR) remission at Week 52
2. Key secondary: sustained DAS28(ESR) LDA at Week 52
3. ACR50 response at Week 52 in relation to Baseline
4. Change from Baseline in HAQ-DI at Week 52
5. Change from Baseline in mTSS at Week 52

| | |
|---|--|
| Comparison groups | Placebo + Methotrexate (Full Analysis Set) v Certolizumab Pegol + Methotrexate (Full Analysis Set) |
| Number of subjects included in analysis | 868 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.023 ^[4] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.446 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.052 |
| upper limit | 1.989 |

Notes:

[4] - The Odds ratio was estimated from a logistic regression model including terms for treatment, region and stratification factor. Nonresponder imputation (NRI) was used.

Secondary: Percentage of subjects meeting the American College of Rheumatology 70 % response criteria (ACR70) at Week 52

| | |
|-----------------|---|
| End point title | Percentage of subjects meeting the American College of Rheumatology 70 % response criteria (ACR70) at Week 52 |
|-----------------|---|

End point description:

The assessments are based on a 70 % or greater improvement from Baseline in the number of tender joints, a 70 %, or more improvement in the number of swollen joints, and a 70 % or greater

improvement in 3 of the 5 remaining core set measures: Patient's Global Assessment of Disease Activity (PtGADA), Physician's Global Assessment of Disease Activity (PhGADA), Patient's Assessment of Arthritis Pain (PtAAP), physical function as assessed by the Health Assessment Questionnaire - Disability Index (HAQ-DI) and C-Reactive Protein (CRP).

| | |
|-----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline (Week 0) to Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 39.9 | 51.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects meeting the 2011 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) remission criteria at Week 52

| | |
|-----------------|--|
| End point title | Percentage of subjects meeting the 2011 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) remission criteria at Week 52 |
|-----------------|--|

End point description:

The ACR/EULAR 2011 remission criteria is defined as:

Tender Joint Count (TJC) ≤ 1 , Swollen Joint Count (SJC) ≤ 1 , C-reactive protein (CRP) ≤ 1 mg/dl and Patient's Global Assessment of Disease Activity (PtGADA) ≤ 1 .

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 20.7 | 32.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Clinical Disease Activity Index (CDAI) \leq 2.8 at Week 52

| | |
|-----------------|--|
| End point title | Percentage of subjects with Clinical Disease Activity Index (CDAI) \leq 2.8 at Week 52 |
|-----------------|--|

End point description:

CDAI is calculated as the sum of tender joint count (TJC), swollen joint count (SJC), Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm), and Physician's Global Assessment of Disease Activity - Visual Analog Scale (PhGADA-VAS in mm). 28 joints are examined where a lower score indicates less disease activity.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 26.3 | 38.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Simplified Disease Activity Index (SDAI) \leq 3.3 at Week 52

| | |
|-----------------|--|
| End point title | Percentage of subjects with Simplified Disease Activity Index (SDAI) \leq 3.3 at Week 52 |
|-----------------|--|

End point description:

SDAI is calculated as the sum of tender joint count (TJC), swollen joint count (SJC), Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm), Physician's Global Assessment of Disease Activity - Visual Analog Scale (PhGADA-VAS in mm) and C-Reactive Protein (CRP in mg/L). 28 joints are examined where a lower score indicates less disease activity.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 24.9 | 38.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) < 2.6 at Week 52

| | |
|-----------------|---|
| End point title | Percentage of subjects with Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) < 2.6 at Week 52 |
|-----------------|---|

End point description:

DAS28[ESR] is calculated using the Tender Joint Count (TJC), Swollen Joint Count (SJC) Erythrocyte Sedimentation Rate (ESR in mm/hour), and the Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm) using the following formula:

$0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \log_{10}(ESR) + 0.014 \times PtGADA$,
where 28 joints are examined and a lower score indicates less disease activity.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 26.8 | 42.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects meeting the 2011 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) remission criteria simplified for clinical practice at Week 52

| | |
|-----------------|---|
| End point title | Percentage of subjects meeting the 2011 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) remission criteria simplified for clinical practice at Week 52 |
|-----------------|---|

End point description:

The 2011 ACR/EULAR remission criteria simplified for clinical practice is defined as:

Tender Joint Count (TJC) ≤ 1 , Swollen Joint Count (SJC) ≤ 1 and Patient's Global Assessment of Disease Activity (PtGADA) ≤ 1 .

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 24.9 | 35.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving a good or moderate European League Against Rheumatism (EULAR) response at Week 52

| | |
|-----------------|--|
| End point title | Percentage of subjects achieving a good or moderate European League Against Rheumatism (EULAR) response at Week 52 |
|-----------------|--|

End point description:

Good response is defined as:

DAS28[ESR] ≤ 3.2 and decrease from Baseline by > 1.2 ;

moderate response is defined as achievement of one of the following:

- DAS28[ESR] ≤ 3.2 and decrease from Baseline > 0.6 and ≤ 1.2
- DAS28[ESR] > 3.2 and ≤ 5.1 and decrease from Baseline > 0.6
- DAS28[ESR] > 5.1 and decrease from Baseline > 1.2 .

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Week 0) to Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 82.2 | 89.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) to Week 52

| | |
|-----------------|---|
| End point title | Change from Baseline in Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) to Week 52 |
|-----------------|---|

End point description:

DAS28[ESR] is calculated using the Tender Joint Count (TJC), Swollen Joint Count (SJC) Erythrocyte Sedimentation Rate (ESR in mm/hour), and the Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm) using the following formula:

$0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \log_{\text{nat}}(\text{ESR}) + 0.014 \times \text{PtGADA}$,

where 28 joints are examined and a lower score indicates less disease activity.

A negative value in DAS28[ESR] change from Baseline indicates an improvement from Baseline.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Week 0) to Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 210 | 646 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | | | | |
| least squares mean (standard error) | -3.014 (\pm 0.109) | -3.615 (\pm 0.069) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Disease Activity Index (CDAI) to Week 52

| | |
|--|---|
| End point title | Change from Baseline in Clinical Disease Activity Index (CDAI) to Week 52 |
| End point description: CDAI is calculated as the sum of tender joint count (TJC), swollen joint count (SJC), Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm), and Physician's Global Assessment of Disease Activity - Visual Analog Scale (PhGADA-VAS in mm). 28 joints are examined where a lower score indicates less disease activity. A negative value in CDAI change from Baseline indicates an improvement from Baseline. | |
| End point type | Secondary |
| End point timeframe: From Baseline (Week 0) to Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 210 | 644 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | | | | |
| least squares mean (standard error) | -29.09 (\pm 0.84) | -33.11 (\pm 0.52) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Simplified Disease Activity Index (SDAI) to Week 52

| | |
|---|---|
| End point title | Change from Baseline in Simplified Disease Activity Index (SDAI) to Week 52 |
| End point description: SDAI is calculated as the sum of tender joint count (TJC), swollen joint count (SJC), Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS in mm), Physician's Global Assessment of Disease Activity - Visual Analog Scale (PhGADA-VAS in mm) and C-Reactive Protein (CRP in mg/L). 28 joints are examined where a lower score indicates less disease activity. A negative value in SDAI change from Baseline indicates an improvement from Baseline. | |
| End point type | Secondary |
| End point timeframe: From Baseline (Week 0) to Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 210 | 644 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | | | | |
| least squares mean (standard error) | -30.24 (± 0.88) | -34.55 (± 0.55) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with a Health Assessment Questionnaire- Disability Index (HAQ-DI) ≤ 0.5 at Week 52

| | |
|--|---|
| End point title | Percentage of subjects with a Health Assessment Questionnaire- Disability Index (HAQ-DI) ≤ 0.5 at Week 52 |
| End point description: | |
| Normative physical function is defined as HAQ-DI score ≤ 0.5. | |
| The domains of the HAQ-DI are dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. | |
| The total score ranges from 0 to 3 with lower scores meaning lower disability. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 35.7 | 48.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Health Assessment Questionnaire - Disability Index (HAQ-DI) to Week 52

| | |
|-----------------|--|
| End point title | Change from Baseline in the Health Assessment Questionnaire - Disability Index (HAQ-DI) to Week 52 |
|-----------------|--|

End point description:

The domains of the HAQ-DI are dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities.

The total score ranges from 0 (no difficulty) to 3 (unable to do) with lower scores meaning lower disability.

A negative value in HAQ-DI change from Baseline indicates an improvement from Baseline.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Week 0) to Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 210 | 645 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | | | | |
| least squares mean (standard error) | -0.819 (± 0.044) | -0.997 (± 0.028) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|----------------------------|------------------------|

Statistical analysis description:

In order to control the overall study-wise Type I error rate at 5 %, hypothesis testing was performed in the following hierarchical order (each at a 2-sided 95 % alpha level):

1. Primary: sustained DAS28(ESR) remission at Week 52
2. Key secondary: sustained DAS28(ESR) LDA at Week 52
3. ACR50 response at Week 52 in relation to Baseline
4. Change from Baseline in HAQ-DI at Week 52
5. Change from Baseline in mTSS at Week 52

| | |
|---|--|
| Comparison groups | Placebo + Methotrexate (Full Analysis Set) v Certolizumab Pegol + Methotrexate (Full Analysis Set) |
| Number of subjects included in analysis | 855 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[5] |
| Method | ANCOVA |
| Parameter estimate | Difference in Least Squares (LS) Means |
| Point estimate | -0.177 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.273 |
| upper limit | -0.082 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.049 |

Notes:

[5] - The CfB in HAQ-DI at Week 52 was analyzed using an ANCOVA model with terms for treatment, region, and time since Rheumatoid Arthritis (RA) diagnosis at Baseline (≤ 4 months or >4 months) as factors and Baseline value as a covariate.

Secondary: Change from Baseline in the Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire (BRAFM-DQ) total score to Week 52

| | |
|-----------------|--|
| End point title | Change from Baseline in the Bristol Rheumatoid Arthritis Fatigue- Multidimensional Questionnaire (BRAFM-DQ) total score to Week 52 |
|-----------------|--|

End point description:

BRAFM-DQ total score ranges from 0 to 70 (with higher scores indicating worse fatigue).
A negative value in BRAFM-DQ change from Baseline indicates an improvement from Baseline.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Week 0) to Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 205 | 636 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | | | | |
| least squares mean (standard error) | -15.6 (± 1) | -17.8 (± 0.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of work days missed (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52

| | |
|-----------------|--|
| End point title | Number of work days missed (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52 |
|-----------------|--|

End point description:

Number of work days missed in the last month for employed subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 52

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 106 | 351 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 0.9 (± 2.5) | 0.6 (± 2.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of work days with reduced productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52

| | |
|------------------------|---|
| End point title | Number of work days with reduced productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52 |
| End point description: | Number of work days with reduced productivity in the last month for employed subjects. |
| End point type | Secondary |
| End point timeframe: | Week 52 |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 106 | 351 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 1.8 (± 4.7) | 1 (± 3.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Interference with work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52

| | |
|------------------------|--|
| End point title | Interference with work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52 |
| End point description: | The Arthritis interference in the last month with work productivity is measured on a scale that ranges from 0 (no interference) to 10 (complete interference) for employed subjects. |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 106 | 351 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 1.9 (± 2.3) | 1.4 (± 2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with no household work (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52

| | |
|--|---|
| End point title | Number of days with no household work (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52 |
| End point description: | |
| Number of days with no household work in the last month. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 206 | 640 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 3 (± 6.7) | 1.9 (± 5.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with reduced household work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52

| | |
|--|---|
| End point title | Number of days with reduced household work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52 |
| End point description: Number of days with reduced household work productivity in the last month. | |
| End point type | Secondary |
| End point timeframe: Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 206 | 640 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 3 (± 6.6) | 2.1 (± 5.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with hired outside help (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52

| | |
|---|--|
| End point title | Number of days with hired outside help (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52 |
| End point description: Number of days with hired outside help in the last month. | |
| End point type | Secondary |
| End point timeframe: Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 206 | 640 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 0.7 (± 3.3) | 0.6 (± 3.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days missed of family/social/leisure activities (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52

| | |
|------------------------|---|
| End point title | Number of days missed of family/social/leisure activities (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52 |
| End point description: | Number of days missed of family/social/leisure activities in the last month. |
| End point type | Secondary |
| End point timeframe: | Week 52 |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 206 | 640 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 0.9 (± 3.1) | 0.9 (± 3.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Interference with household work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52

| | |
|------------------------|--|
| End point title | Interference with household work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 52 |
| End point description: | The Arthritis interference in the last month with household work productivity is measured on a scale that ranges from 0 (no interference) to 10 (complete interference). |
| End point type | Secondary |
| End point timeframe: | Week 52 |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 206 | 640 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 2.5 (± 2.8) | 1.9 (± 2.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Low Disease Activity (LDA) at Week 52

| | |
|---|--|
| End point title | Percentage of subjects achieving Low Disease Activity (LDA) at Week 52 |
| End point description: LDA is defined as achieving a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2. | |
| End point type | Secondary |
| End point timeframe: Week 52 | |

| End point values | Placebo + Methotrexate (Full Analysis Set) | Certolizumab Pegol + Methotrexate (Full Analysis Set) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 213 | 655 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 39.4 | 54.7 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Screening over Baseline (Week 0) and Treatment Period 1 (Week 2 to Week 52) to the Safety Follow-Up Visit.

Adverse event reporting additional description:

Adverse Events presented below refer to the Safety Set 1 (SS1), which consisted of all subjects in the Randomized Set who had received at least 1 dose of study medication (CZP/PBO) in Period 1.

| | |
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| Assessment type | Non-systematic |
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Dictionary used

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| Dictionary name | MedDRA |
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| Dictionary version | 17.0 |
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Reporting groups

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|-----------------------|------------------------|
| Reporting group title | Placebo + Methotrexate |
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Reporting group description:

Placebo + Methotrexate (MTX)

2 syringes Placebo at Baseline, Week 2 and Week 4 + MTX, followed by 1 syringe Placebo every 2 Weeks + MTX.

The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

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|-----------------------|-----------------------------------|
| Reporting group title | Certolizumab Pegol + Methotrexate |
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Reporting group description:

Certolizumab Pegol + Methotrexate (MTX)

Prefilled syringes containing an injectable volume of 1 ml of solution for injection CZP for single use at a dosage strength of 200 mg/ml.

Injections will be given subcutaneously. CZP 400 mg + MTX at Baseline, Week 2 and Week 4, followed by a maintenance dose of CZP 200 mg + MTX every 2 Weeks until Week 50.

The MTX treatment is to be initiated at a dose of 10 mg per Week. The MTX dosage should be escalated by 5 mg every 2 Weeks such that the maximum dosage of 25 mg per Week is achieved by Week 6 to Week 8.

| Serious adverse events | Placebo + Methotrexate | Certolizumab Pegol + Methotrexate | |
|---|---------------------------|--------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 217 (9.22%) | 70 / 659 (10.62%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervix carcinoma | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chondrosarcoma | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cancer | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Coronary arterial stent insertion | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leg amputation | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food allergy | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 659 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Epiglottic cyst | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 659 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal polyp | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 659 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 3 / 659 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow toxicity | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 659 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erosive duodenitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric panniculitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 659 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Bladder outlet obstruction | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| Renal failure | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lupus-like syndrome | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 4 / 659 (0.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid nodule | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| Appendiceal abscess | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast abscess | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 2 / 659 (0.30%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin abscess | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impetigo | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Labyrinthitis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 659 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Latent tuberculosis | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 217 (1.38%) | 4 / 659 (0.61%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis gastrointestinal | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 659 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo + Methotrexate | Certolizumab Pegol + Methotrexate | |
|---|-----------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 63 / 217 (29.03%) | 248 / 659 (37.63%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 9 / 217 (4.15%) | 42 / 659 (6.37%) | |
| occurrences (all) | 13 | 46 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 8 / 217 (3.69%) | 45 / 659 (6.83%) | |
| occurrences (all) | 11 | 65 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 22 / 217 (10.14%) | 83 / 659 (12.59%) | |
| occurrences (all) | 22 | 92 | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 11 / 217 (5.07%) | 72 / 659 (10.93%) | |
| occurrences (all) | 12 | 86 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 16 / 217 (7.37%) | 48 / 659 (7.28%) | |
| occurrences (all) | 18 | 63 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 217 (5.99%) | 46 / 659 (6.98%) | |
| occurrences (all) | 17 | 60 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 July 2012 | <p>At the time of Global Protocol Amendment 1 (27 Jul 2012), enrollment was ongoing. The main change covered in this amendment was the incorporation of the updated UCB tuberculosis (TB) detection and monitoring policy. The recent changes in national guidelines recommended different TB testing (QuantiFERON®-TB GOLD test or purified protein derivative [PPD] Skin test) as the preferred test in a number of geographies. Therefore, this amendment offered the option for Investigators to stay within local guidelines and regulations. Also, some national guidelines were recommending different protocols of prophylactic treatment for latent TB. Thus, this amendment addressed these changes and gave Investigators the possibility to be compliant with current guidelines and regulations.</p> <p>Several other minor changes and clarifications were incorporated into Global Protocol Amendment 1. Those affecting study conduct included:</p> <ul style="list-style-type: none">- Stipulation for contraception use was extended from 10 weeks to at least 3 months (USA/Canada) or 6 months (Europe, Australia, and Latin America) after the last dose of study treatment. Similarly, the exclusion criterion was extended from 10 weeks to 6 months for female subjects who were breastfeeding, pregnant, or planned to become pregnant during the study or within 6 months following last dose of study treatment.- The Screening Period length was clarified.- MTX packaging and labeling were clarified.- Rescreening of subjects was clarified. |
| 06 February 2013 | <p>At the time of Global Protocol Amendment 2 (06 Feb 2013), enrollment was ongoing. The main changes covered in this amendment were:</p> <ul style="list-style-type: none">- The PBO+MTX arm of Period 1 was prolonged in Period 2 until Week 104 to provide subjects extended treatment benefit with the treatment combination PBO+MTX. These subjects were in sustained LDA when reaching Week 52 and the subjects have at any time a rescue option available when they flare providing them the initiation of a CZP treatment and a maintenance on CZP until Week 104.- The prolongation of the PBO+MTX arm in Period 2 provided a higher protection of the Period 1 blind by allowing more time to clean the large amount of study data generated.- The prolongation of the PBO+MTX arm in Period 2 provided, as a consequence, additional exploratory data and allowed comparison of the outcomes of an initial treatment with or without CZP in Period 1 over a longer time.- Following the Statistical Analysis Plan (SAP) development, some updates were considered in the statistical section.- PBO+MTX nomenclature was replaced by MTX+CZP stopped dosing in sections related to Period 2.- The serious AE (SAE) reporting details were changed, an e-mail address was added. All other safety-related questions were to be addressed to the Study Physician or Medical Monitors assigned to the study. |
| 13 January 2014 | <p>At the time of Global Protocol Amendment 3 (13 Jan 2014), all subjects were enrolled. The main changes covered in this amendment were:</p> <ul style="list-style-type: none">- TB language was expanded to reflect current UCB guidelines.- Additional endpoints in Period 1 and Period 2 and associated analyses of minimum clinically important differences (MCID) from Baseline in various assessment tools were added.- A change in wording in laboratory analyses from inorganic phosphorous to phosphorous.- Clarification on PK analyses was made to include CZP moiety analyses.- Additional subgroups of age, rheumatoid factor (RF), albumin, and presence of erosions at Baseline were considered for analyses.- Predictability analyses were added.- A Completer Set for Period 1 and associated sensitivity analyses were added.- Details on multiple comparisons/multiplicity were added. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported