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
SAE, non-fatal + AE, non-serious non-fatal	2	1
Lack of efficacy	16	20
Protocol deviation	6	19

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:
$0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \text{lognat (ESR)} + 0.014 \times \text{PtGADA}$,
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) ≤ 2.8 at Week 52

End point title	Percentage of subjects with Clinical Disease Activity Index (CDAI) ≤ 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) ≤ 3.3 at Week 52

End point title	Percentage of subjects with Simplified Disease Activity Index (SDAI) ≤ 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:
$0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \text{lognat (ESR)} + 0.014 \times \text{PtGADA}$,
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:
$0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \text{lognat (ESR)} + 0.014 \times \text{PtGADA}$,
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 (± 0.109)	-3.615 (± 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 (± 0.84)	-33.11 (± 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 (BRAF-MDQ) total score to Week 52

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

End point description:

BRAF-MDQ total score ranges from 0 to 70 (with higher scores indicating worse fatigue).
A negative value in BRAF-MDQ 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.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

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.

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			

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	

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			

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			

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			

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			

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			

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			

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	

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	

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	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. Several other minor changes and clarifications were incorporated into Global Protocol Amendment 1. Those affecting study conduct included: - 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	At the time of Global Protocol Amendment 2 (06 Feb 2013), enrollment was ongoing. The main changes covered in this amendment were: - 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	At the time of Global Protocol Amendment 3 (13 Jan 2014), all subjects were enrolled. The main changes covered in this amendment were: - 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