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

Summary

EudraCT number	2011-001729-25
Trial protocol	BE DE IE HU ES CZ AT SE NL IT GB
Global end of trial date	10 September 2015

Results information

Result version number	v3
This version publication date	22 July 2016
First version publication date	24 July 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	RA0055 Period 2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01521923
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, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 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	Final
Date of interim/final analysis	13 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate that both CZP + MTX dosing frequencies (the standard maintenance dose CZP 200 mg every 2 weeks + MTX and the reduced frequency maintenance dose CZP 200 mg every 4 weeks + MTX) are superior to PBO + MTX in maintaining subjects in LDA at Week 104

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: 16
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 77
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 71

Worldwide total number of subjects	357
EEA total number of subjects	222

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)	312
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in January 2012.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set 2 (SS2) which consists of all subjects randomized into Period 1 who had received at least 1 dose of study medication (CZP/PBO) in Period 2.

Period 1

Period 1 title	Period 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	PBO+MTX / PBO+MTX

Arm description:

Placebo (PBO) + Methotrexate (MTX) in Period 1

1 syringe PBO every 2 Weeks + MTX in Period 2

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

Dosage and administration details:

Subcutaneous injections every 2 Weeks or every 4 Weeks

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:

A dose of at least 15 mg per Week had to be taken to remain in the study. MTX was given every week from Week 52 onwards until Week 103

Arm title	CZP+MTX / PBO+MTX

Arm description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe PBO every 2 Weeks + MTX in Period 2

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

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or every 4 Weeks

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:

A dose of at least 15 mg per Week had to be taken to remain in the study. MTX was given every week from Week 52 onwards until Week 103

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

Dosage and administration details:

Subcutaneous injections every 2 Weeks or every 4 Weeks

Arm title	CZP+MTX / CZP Q4W+MTX

Arm description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 4 Weeks/ 1 syringe Placebo (PBO) every 4 Weeks (CZP and PBO administration to be staggered 2 weeks apart to maintain blind) + MTX in Period 2

Arm type	Experimental
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:

A dose of at least 15 mg per Week had to be taken to remain in the study. MTX was given every week from Week 52 onwards until Week 103

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

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or every 4 Weeks

Arm title	CZP+MTX / CZP Q2W+MTX

Arm description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 2 Weeks + MTX in Period 2

Arm type	Experimental
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:

A dose of at least 15 mg per Week had to be taken to remain in the study. MTX was given every week from Week 52 onwards until Week 103

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

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or every 4 Weeks

Number of subjects in period 1	PBO+MTX / PBO+MTX	CZP+MTX / PBO+MTX	CZP+MTX / CZP Q4W+MTX
Started	66	81	127
Completed	59	72	112
Not completed	7	9	15
AE, serious fatal	1	-	-
Consent withdrawn by subject	1	1	1
Other	2	1	3
AE, non-serious, non-fatal	1	3	6
AE, captured in Period 1	-	1	-
Lost to follow-up	1	-	2
SAE, non-fatal	-	2	2
SAE, non-fatal + AE, non-serious nonfatal	-	-	-
Lack of efficacy	1	1	-
Protocol deviation	-	-	1

Number of subjects in period 1	CZP+MTX / CZP Q2W+MTX
Started	83
Completed	70
Not completed	13
AE, serious fatal	-
Consent withdrawn by subject	2
Other	6
AE, non-serious, non-fatal	2
AE, captured in Period 1	1
Lost to follow-up	1
SAE, non-fatal	-
SAE, non-fatal + AE, non-serious nonfatal	1
Lack of efficacy	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	PBO+MTX / PBO+MTX
Reporting group description:	
Placebo (PBO) + Methotrexate (MTX) in Period 1 1 syringe PBO every 2 Weeks + MTX in Period 2	
Reporting group title	CZP+MTX / PBO+MTX
Reporting group description:	
Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1 1 syringe PBO every 2 Weeks + MTX in Period 2	
Reporting group title	CZP+MTX / CZP Q4W+MTX
Reporting group description:	
Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1 1 syringe 200 mg Certolizumab pegol (CZP) every 4 Weeks/ 1 syringe Placebo (PBO) every 4 Weeks (CZP and PBO administration to be staggered 2 weeks apart to maintain blind) + MTX in Period 2	
Reporting group title	CZP+MTX / CZP Q2W+MTX
Reporting group description:	
Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1 1 syringe 200 mg Certolizumab pegol (CZP) every 2 Weeks + MTX in Period 2	

Reporting group values	PBO+MTX / PBO+MTX	CZP+MTX / PBO+MTX	CZP+MTX / CZP Q4W+MTX
Number of subjects	66	81	127
Age Categorical Units: Subjects			
<=18 years	0	0	2
Adults (18-64 years)	54	70	114
>=65 years	12	11	11
Age Continuous Units: years			
arithmetic mean	51.2	47.9	49.1
standard deviation	± 13.7	± 14.1	± 12.5
Gender Categorical Units: Subjects			
Male	12	22	40
Female	54	59	87

Reporting group values	CZP+MTX / CZP Q2W+MTX	Total	
Number of subjects	83	357	
Age Categorical Units: Subjects			
<=18 years	0	2	
Adults (18-64 years)	72	310	
>=65 years	11	45	

Age Continuous Units: years			
arithmetic mean	49.1		
standard deviation	± 13.2	-	
Gender Categorical Units: Subjects			
Male	18	92	
Female	65	265	

End points

End points reporting groups

Reporting group title	PBO+MTX / PBO+MTX

Reporting group description:

Placebo (PBO) + Methotrexate (MTX) in Period 1

1 syringe PBO every 2 Weeks + MTX in Period 2

Reporting group title	CZP+MTX / PBO+MTX

Reporting group description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe PBO every 2 Weeks + MTX in Period 2

Reporting group title	CZP+MTX / CZP Q4W+MTX

Reporting group description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 4 Weeks/ 1 syringe Placebo (PBO) every 4 Weeks (CZP and PBO administration to be staggered 2 weeks apart to maintain blind) + MTX in Period 2

Reporting group title	CZP+MTX / CZP Q2W+MTX

Reporting group description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 2 Weeks + MTX in Period 2

Subject analysis set title	CZP+MTX / PBO+MTX (Full Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe PBO every 2 Weeks + MTX in Period 2

Subject analysis set title	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 4 Weeks/ 1 syringe Placebo (PBO) every 4 Weeks (CZP and PBO administration to be staggered 2 weeks apart to maintain blind) + MTX in Period 2

Subject analysis set title	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 2 Weeks + MTX in Period 2

Subject analysis set title	CZP+MTX / PBO+MTX (Radiographic Set)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe PBO every 2 Weeks + MTX in Period 2

Subject analysis set title	CZP+MTX / CZP Q4W+MTX (Radiographic Set)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 4 Weeks/ 1 syringe Placebo (PBO) every 4 Weeks (CZP and PBO administration to be staggered 2 weeks apart to maintain blind) + MTX in Period 2

Subject analysis set title	CZP+MTX / CZP Q2W+MTX (Radiographic Set)

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200mg Certolizumab pegol (CZP) every 2 Weeks + MTX in Period 2

Primary: Percentage of subjects with Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) <= 3.2 at Week 104 in RA0055 Period 2 without flaring

End point title	Percentage of subjects with Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) <= 3.2 at Week 104 in RA0055 Period 2 without flaring

End point description:

This Outcome Measure includes all subjects that have a DAS28 [ESR] <= 3.2 from the start of RA0055 Period 2 (Week 52 of RA0055 Period 1) to Week 104 in RA0055 Period 2 without flaring.

End point type	Primary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Maintained LDA	39.2	53.2	48.8	

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 a hierarchical order beginning with the CZP standard maintenance dosing (200 mg Q2W) + MTX group vs the CZP stopped dosing (PBO) + MTX group. If this analysis was statistically significant at the alpha = 0.05 level, an additional comparison of the CZP reduced frequency dosing (200 mg Q4W) + MTX group vs the CZP stopped dosing + MTX group was performed with testing at the alpha = 0.05 level

Comparison groups	CZP+MTX / PBO+MTX (Full Analysis Set) v CZP+MTX / CZP Q2W+MTX (Full Analysis Set)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.112
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.719

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.881
upper limit	3.354

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 a hierarchical order. A hierarchical test procedure was applied to protect the Overall significance level for the multiplicity of endpoints. Hypothesis testing was performed in the following predefined order, each at a 2-sided 95 % alpha level

Comparison groups	CZP+MTX / PBO+MTX (Full Analysis Set) v CZP+MTX / CZP Q4W+MTX (Full Analysis Set)
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.889
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.026
upper limit	3.48

Secondary: Percentage of subjects with Disease Activity Score 28 [ESR] (DAS28 [ESR]) < 2.6 at Week 52 in previous study RA0055 Period 1 who maintain a DAS28 [ESR] < 2.6 from Week 52 in RA0055 Period 1 through Week 104 in RA0055 Period 2 without flaring

End point title	Percentage of subjects with Disease Activity Score 28 [ESR] (DAS28 [ESR]) < 2.6 at Week 52 in previous study RA0055 Period 1 who maintain a DAS28 [ESR] < 2.6 from Week 52 in RA0055 Period 1 through Week 104 in RA0055 Period 2 without flaring

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 x √(TJC) + 0.28 x √(SJC) + 0.70 x lognat (ESR) + 0.014 x PtGADA, where 28 joints are examined and a lower score indicates less disease activity.

End point type	Secondary

End point timeframe:

From Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	51	83	50	
Units: percentage of subjects				
number (not applicable)				
Maintained Remitter	33.3	43.4	44	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in previous study RA0055 Period 1 in modified Total Sharp Score (mTSS) to Week 104 in RA0055 Period 2

End point title	Change from Baseline in previous study RA0055 Period 1 in modified Total Sharp Score (mTSS) to Week 104 in RA0055 Period 2

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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Radiographic Set)	CZP+MTX / CZP Q4W+MTX (Radiographic Set)	CZP+MTX / CZP Q2W+MTX (Radiographic Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	113	72	
Units: units on a scale				
median (full range (min-max))				
median (full range)	0 (-5 to 28)	0 (-9 to 9)	0 (-2 to 9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 52 in previous study RA0055 Period 1 in modified Total Sharp Score (mTSS) to Week 104 in RA0055 Period 2

End point title	Change from Week 52 in previous study RA0055 Period 1 in modified Total Sharp Score (mTSS) to Week 104 in RA0055 Period 2

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 Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Radiographic Set)	CZP+MTX / CZP Q4W+MTX (Radiographic Set)	CZP+MTX / CZP Q2W+MTX (Radiographic Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	113	72	
Units: units on a scale				
median (full range (min-max))				
median (full range)	0 (-3 to 50)	0 (-9 to 7)	0 (-4 to 4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with radiographic non-progression from Baseline in previous study RA0055 Period 1 to Week 104 in RA0055 Period 2

End point title	Percentage of subjects with radiographic non-progression from Baseline in previous study RA0055 Period 1 to Week 104 in RA0055 Period 2

End point description:

Radiographic nonprogression is defined as change in modified Total Sharp Score (mTSS) <= 0.5.

End point type	Secondary

End point timeframe:

From Baseline (Week 0) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Radiographic Set)	CZP+MTX / CZP Q4W+MTX (Radiographic Set)	CZP+MTX / CZP Q2W+MTX (Radiographic Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	113	72	
Units: percentage of subjects				
number (not applicable)				
Subjects with Nonprogression	69.3	77.9	79.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with radiographic non-progression from Week 52 in previous study RA0055 Period 1 to Week 104 in RA0055 Period 2

End point title	Percentage of subjects with radiographic non-progression from Week 52 in previous study RA0055 Period 1 to Week 104 in RA0055 Period 2

End point description:

Radiographic nonprogression is defined as change in modified Total Sharp Score (mTSS) <= 0.5.

End point type	Secondary

End point timeframe:

From Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Radiographic Set)	CZP+MTX / CZP Q4W+MTX (Radiographic Set)	CZP+MTX / CZP Q2W+MTX (Radiographic Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	113	72	
Units: percentage of subjects				
number (not applicable)				
Subjects with Nonprogression	80	84.1	90.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in previous study RA0055 Period 1 in the joint erosion score to Week 104 in RA0055 Period 2

End point title	Change from Baseline in previous study RA0055 Period 1 in the joint erosion score to Week 104 in RA0055 Period 2

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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Radiographic Set)	CZP+MTX / CZP Q4W+MTX (Radiographic Set)	CZP+MTX / CZP Q2W+MTX (Radiographic Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	113	72	
Units: units on a scale				
median (full range (min-max))				
median (full range)	0 (-4 to 18)	0 (-8 to 7)	0 (-2 to 9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 52 in previous study RA0055 Period 1 in the joint erosion score to Week 104 in RA0055 Period 2

End point title	Change from Week 52 in previous study RA0055 Period 1 in the joint erosion score to Week 104 in RA0055 Period 2

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 Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Radiographic Set)	CZP+MTX / CZP Q4W+MTX (Radiographic Set)	CZP+MTX / CZP Q2W+MTX (Radiographic Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	113	72	
Units: units on a scale				
median (full range (min-max))				
median (full range)	0 (-3 to 36)	0 (-8 to 5)	0 (-2 to 4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in previous study RA0055 Period 1 in the joint narrowing score to Week 104 in RA0055 Period 2

End point title	Change from Baseline in previous study RA0055 Period 1 in the joint narrowing score to Week 104 in RA0055 Period 2

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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Radiographic Set)	CZP+MTX / CZP Q4W+MTX (Radiographic Set)	CZP+MTX / CZP Q2W+MTX (Radiographic Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	113	72	
Units: units on a scale				
median (full range (min-max))				
median (full range)	0 (-3 to 12)	0 (-4 to 4)	0 (-2 to 2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 52 in previous study RA0055 Period 1 in the joint narrowing score to Week 104 in RA0055 Period 2

End point title	Change from Week 52 in previous study RA0055 Period 1 in the joint narrowing score to Week 104 in RA0055 Period 2

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 Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Radiographic Set)	CZP+MTX / CZP Q4W+MTX (Radiographic Set)	CZP+MTX / CZP Q2W+MTX (Radiographic Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	75	113	72	
Units: units on a scale				
median (full range (min-max))				
median (full range)	0 (-2 to 14)	0 (-3 to 5)	0 (-4 to 2)	

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 104 in RA0055 Period 2

End point title	Percentage of subjects meeting the American College of Rheumatology 20 % response criteria (ACR20) at Week 104 in RA0055 Period 2

End point description:

The assessments are based on a 20 % or greater improvement from Baseline in previous study RA0055 Period 1 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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Responder	74.7	86.5	73.8	

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 104 in RA0055 Period 2

End point title	Percentage of subjects meeting the American College of Rheumatology 50 % response criteria (ACR50) at Week 104 in RA0055 Period 2

End point description:

The assessments are based on a 50 % or greater improvement from Baseline in previous study RA0055 Period 1 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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Responder	68.4	80.2	71.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects meeting the American College of Rheumatology 70 % response criteria (ACR70) at Week 104 in RA0055 Period 2

End point title	Percentage of subjects meeting the American College of Rheumatology 70 % response criteria (ACR70) at Week 104 in RA0055 Period 2

End point description:

The assessments are based on a 70 % or greater improvement from Baseline in previous study RA0055 Period 1 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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Responder	60.8	70.6	63.1	

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 104 in RA0055 Period 2

End point title	Percentage of subjects meeting the 2011 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) remission criteria at Week 104 in RA0055 Period 2

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) <= 10 mm.

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Remitter	34.2	52.4	46.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Clinical Disease Activity Index (CDAI) <= 2.8 at Week 104 in RA0055 Period 2

End point title	Percentage of subjects with Clinical Disease Activity Index (CDAI) <= 2.8 at Week 104 in RA0055 Period 2

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 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Remitter	43	55.6	52.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Simplified Disease Activity Index (SDAI) <= 3.3 at Week 104 in RA0055 Period 2

End point title	Percentage of subjects with Simplified Disease Activity Index (SDAI) <= 3.3 at Week 104 in RA0055 Period 2

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 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Remitter	41.8	57.1	53.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28[ESR]) < 2.6 at Week 104 in RA0055 Period 2

End point title	Percentage of subjects with Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28[ESR]) < 2.6 at Week 104 in RA0055 Period 2

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 x √(TJC) + 0.28 x √(SJC) + 0.70 x lognat (ESR) + 0.014 x PtGADA, where 28 joints are examined and a lower score indicates less disease activity.

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Remitter	44.3	63.5	52.4	

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 104 in RA0055 Period 2

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 104 in RA0055 Period 2

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) <= 10 mm.

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Remitter	35.4	52.4	50	

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 104 in RA0055 Period 2

End point title	Percentage of subjects achieving a good or moderate European League Against Rheumatism (EULAR) response at Week 104 in RA0055 Period 2

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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Good or Moderate Response	88.6	98.4	94	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in previous study RA0055 Period 1 in Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) to Week 104 in RA0055 Period 2

End point title	Change from Baseline in previous study RA0055 Period 1 in Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) to Week 104 in RA0055 Period 2

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 x √(TJC) + 0.28 x √(SJC) + 0.70 x lognat (ESR) + 0.014 x 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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-3.436 (± 1.711)	-4.252 (± 1.275)	-3.901 (± 1.546)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 52 in previous study RA0055 Period 1 in Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) to Week 104 in RA0055 Period 2

End point title	Change from Week 52 in previous study RA0055 Period 1 in Disease Activity Score [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) to Week 104 in RA0055 Period 2

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 x √(TJC) + 0.28 x √(SJC) + 0.70 x lognat (ESR) + 0.014 x 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 Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: units on a scale				
arithmetic mean (standard deviation)				

mean (standard deviation)	1.145 (± 1.372)	0.414 (± 1.033)	0.511 (± 1.215)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in previous study RA0055 Period 1 in Clinical Disease Activity Index (CDAI) to Week 104 in RA0055 Period 2

End point title	Change from Baseline in previous study RA0055 Period 1 in Clinical Disease Activity Index (CDAI) to Week 104 in RA0055 Period 2

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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: units on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-30.7 (± 16.4)	-37.2 (± 12.1)	-32.6 (± 15.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 52 in previous study RA0055 Period 1 in Clinical Disease Activity Index (CDAI) to Week 104 in RA0055 Period 2

End point title	Change from Week 52 in previous study RA0055 Period 1 in Clinical Disease Activity Index (CDAI) to Week 104 in RA0055 Period 2

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 Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: units on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	6 (± 10.4)	1.7 (± 5.9)	2.5 (± 7.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in previous study RA0055 Period 1 in Simplified Disease Activity Index (SDAI) to Week 104 in RA0055 Period 2

End point title	Change from Baseline in previous study RA0055 Period 1 in Simplified Disease Activity Index (SDAI) to Week 104 in RA0055 Period 2

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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: units on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-31.6 (± 17.4)	-39.1 (± 13.5)	-34.3 (± 16.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 52 in previous study RA0055 Period 1 in Simplified Disease Activity Index (SDAI) to Week 104 in RA0055 Period 2

End point title	Change from Week 52 in previous study RA0055 Period 1 in Simplified Disease Activity Index (SDAI) to Week 104 in RA0055 Period 2

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 Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: units on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	6.5 (± 10.9)	1.7 (± 6)	2.6 (± 7.8)	

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 104 in RA0055 Period 2

End point title	Percentage of subjects with a Health Assessment Questionnaire- Disability Index (HAQ-DI) ≤ 0.5 at Week 104 in RA0055 Period 2

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 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
Responder	49.4	63.5	61.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) <= 3.2 at Week 104 in RA0055 Period 2

End point title	Percentage of subjects with Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) <= 3.2 at Week 104 in RA0055 Period 2

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 x √(TJC) + 0.28 x √(SJC) + 0.70 x lognat (ESR) + 0.014 x PtGADA, where 28 joints are examined and a lower score indicates less disease activity.

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
LDA	59.5	73.8	65.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to flare from Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point title	Time to flare from Week 52 in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point description:

Time to flare, defined as an increase of DAS28[ESR] >= 0.6 above Week 52 DAS28[ESR] level, having a DAS28[ESR] >= 3.2 and judged by the Investigator as due to RA and all three criteria confirmed at an additional visit two weeks thereafter, from Week 52 onwards.
Data not available as > 75% of the participants failed to meet flare criteria.
-999/-9999 = not estimable.

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: days				
geometric mean (geometric coefficient of variation)				
Geometic Mean (Geo. Coeff. of Variation)	-999 (± -9999)	-999 (± -9999)	-999 (± -9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in previous study RA0055 Period 1 in the Bristol Rheumatoid Arthritis Fatigue- Multidimensional Questionnaire (BRAF-MDQ) total score to Week 104 in RA0055 Period 2

End point title	Change from Baseline in previous study RA0055 Period 1 in the Bristol Rheumatoid Arthritis Fatigue- Multidimensional Questionnaire (BRAF-MDQ) total score to Week 104 in RA0055 Period 2

End point description:

BRAF-MDQ total score ranges from 0 to 70 (with higher scores indicating worse fatigue), whereas the score for each dimension is different due to the varied number of questions (0 –22 for physical, 0- 21 for living, 0- 15 for cognition, and 0- 12 for emotion). 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) in RA0055 Period 1 to Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-15.9 (± 16.7)	-21.6 (± 16.9)	-20.7 (± 17.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of work days missed (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

End point title	Number of work days missed (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

End point description:

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

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: days				
arithmetic mean (standard deviation)				
mean (standard deviation)	0.5 (± 1.46)	0.2 (± 0.89)	0.3 (± 0.86)	

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 104 in RA0055 Period 2

End point title	Number of work days with reduced productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

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 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	79	51	
Units: days				
arithmetic mean (standard deviation)				
mean (standard deviation)	1.5 (± 4.88)	0.6 (± 2.01)	0.8 (± 2.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Interference with work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

End point title	Interference with work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

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 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	79	51	
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	2.3 (± 2.84)	0.9 (± 1.6)	1.2 (± 2.19)	

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 104 in RA0055 Period 2	
End point title	Number of days with no household work (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2
End point description: Number of days with no household work in the last month.	
End point type	Secondary
End point timeframe: Week 104 in RA0055 Period 2	

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: days				
arithmetic mean (standard deviation)				
mean (standard deviation)	1.4 (± 3.35)	0.7 (± 2.29)	0.8 (± 2.76)	

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 104 in RA0055 Period 2	
End point title	Number of days with reduced household work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2
End point description: Number of days with reduced household work productivity in the last month.	
End point type	Secondary
End point timeframe: Week 104 in RA0055 Period 2	

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: days				
arithmetic mean (standard deviation)				
mean (standard deviation)	1.8 (± 4.49)	0.9 (± 3.01)	1 (± 3.37)	

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 104 in RA0055 Period 2

End point title	Number of days with hired outside help (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

End point description:

Number of days with hired outside help days in the last month.

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: days				
arithmetic mean (standard deviation)				
mean (standard deviation)	0.3 (± 0.98)	0.3 (± 2.7)	0.1 (± 0.45)	

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 104 in RA0055 Period 2

End point title	Number of days missed of family/social/leisure activities (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

End point description:

Number of days missed of family/social/leisure activities in the last month.

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: days				
arithmetic mean (standard deviation)				
mean (standard deviation)	1.2 (± 3.36)	0.2 (± 1.8)	0.2 (± 0.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Interference with household work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

End point title	Interference with household work productivity (Work Productivity Survey - Rheumatoid Arthritis [WPS-RA]) at Week 104 in RA0055 Period 2

End point description:

The Arthritis interference in the last month with household productivity is measured on a scale that ranges from 0 (no interference) to 10 (complete interference).

End point type	Secondary

End point timeframe:

Week 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	2 (± 2.63)	1 (± 1.53)	1.1 (± 1.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Low Disease Activity (LDA) at Week 104 in RA0055 Period 2

End point title	Percentage of subjects achieving Low Disease Activity (LDA) at

	Week 104 in RA0055 Period 2

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 104 in RA0055 Period 2

End point values	CZP+MTX / PBO+MTX (Full Analysis Set)	CZP+MTX / CZP Q4W+MTX (Full Analysis Set)	CZP+MTX / CZP Q2W+MTX (Full Analysis Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	126	84	
Units: percentage of subjects				
number (not applicable)				
LDA	68.4	74.6	70.2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events for Period 2 were collected from the date of the Week 52 study medication up to 70 days after the last (most recent) Certolizumab pegol (CZP) or Placebo (PBO) dose

Adverse event reporting additional description:

For the safety results, the main comparisons of interest are across the 3 CZP re-randomized groups; the PBO+MTX/PBO+MTX group is included for completeness.
For subjects induced/ re-induced with CZP due to flare, only AEs up to the time of induction/re-induction with CZP are included. Note that 3 SAEs occurred after induction/ re-induction.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	PBO+MTX / PBO+MTX

Reporting group description:

Placebo (PBO) + Methotrexate (MTX) in Period 1

1 syringe PBO every 2 Weeks + MTX in Period 2

Reporting group title	CZP+MTX / PBO+MTX

Reporting group description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe PBO every 2 Weeks + MTX in Period 2

Reporting group title	CZP+MTX / CZP Q4W+MTX

Reporting group description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 4 Weeks/ 1 syringe Placebo (PBO) every 4 Weeks (CZP and PBO administration to be staggered 2 weeks apart to maintain blind) + MTX in Period 2

Reporting group title	CZP+MTX / CZP Q2W+MTX

Reporting group description:

Certolizumab pegol (CZP) 200 mg Q2W + Methotrexate (MTX) in Period 1

1 syringe 200 mg Certolizumab pegol (CZP) every 2 Weeks + MTX in Period 2

Serious adverse events	PBO+MTX / PBO+MTX	CZP+MTX / PBO+MTX	CZP+MTX / CZP Q4W+MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 66 (6.06%)	6 / 81 (7.41%)	9 / 127 (7.09%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myxoid liposarcoma			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 66 (0.00%)	2 / 81 (2.47%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 66 (0.00%)	1 / 81 (1.23%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness	Additional description: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included		
subjects affected / exposed[1]	0 / 3 (0.00%)	0 / 10 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical polyp			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Bronchial carcinoma	Additional description: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included		
subjects affected / exposed[2]	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression	Additional description: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included		
subjects affected / exposed[3]	0 / 3 (0.00%)	1 / 10 (10.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial ischaemia			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Intercostal neuralgia			

subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Meniere's disease			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 81 (1.23%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroduodenitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 66 (1.52%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Tendon disorder			
subjects affected / exposed	1 / 66 (1.52%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	1 / 66 (1.52%)	0 / 81 (0.00%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Latent tuberculosis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 81 (1.23%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 81 (1.23%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	CZP+MTX / CZP Q2W+MTX		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 83 (4.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myxoid liposarcoma			

subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Influenza like illness	Additional description: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included		
subjects affected / exposed[1]	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical polyp			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchial carcinoma	Additional description: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included		
subjects affected / exposed[2]	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression	Additional description: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included		

subjects affected / exposed[3]	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial ischaemia			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Intercostal neuralgia			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Meniere's disease			
alternative dictionary used: MedDRA 17.0			

subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastroduodenitis			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Tendon disorder			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis salmonella			

subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Latent tuberculosis			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	0 / 83 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Only subjects who were induced/re-induced with CZP in Period 2 due to flare are included.

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

Non-serious adverse events	PBO+MTX / PBO+MTX	CZP+MTX / PBO+MTX	CZP+MTX / CZP Q4W+MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 66 (4.55%)	13 / 81 (16.05%)	32 / 127 (25.20%)
Infections and infestations			
Urinary tract infection			
alternative dictionary used: MedDRA 17.0			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 66 (1.52%)	2 / 81 (2.47%)	4 / 127 (3.15%)
occurrences (all)	1	2	4
Nasopharyngitis			
subjects affected / exposed	0 / 66 (0.00%)	5 / 81 (6.17%)	13 / 127 (10.24%)
occurrences (all)	0	5	15
Pharyngitis			
subjects affected / exposed	0 / 66 (0.00%)	5 / 81 (6.17%)	5 / 127 (3.94%)
occurrences (all)	0	5	5
Latent tuberculosis			

subjects affected / exposed	0 / 66 (0.00%)	0 / 81 (0.00%)	7 / 127 (5.51%)
occurrences (all)	0	0	7
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	2 / 66 (3.03%)	3 / 81 (3.70%)	8 / 127 (6.30%)
occurrences (all)	3	3	8

Non-serious adverse events	CZP+MTX / CZP Q2W+MTX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 83 (15.66%)		
Infections and infestations			
Urinary tract infection			
alternative dictionary used: MedDRA 17.0			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	4 / 83 (4.82%)		
occurrences (all)	4		
Pharyngitis			
subjects affected / exposed	2 / 83 (2.41%)		
occurrences (all)	2		
Latent tuberculosis			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	2 / 83 (2.41%)		
occurrences (all)	3		

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