Clinical trial results:
A Multicenter, Single-blind, Randomized Parallel-group Study to Assess the Short- and Long-term Efficacy of Certolizumab Pegol Plus Methotrexate Compared to Adalimumab Plus Methotrexate in Subjects With Moderate to Severe Rheumatoid Arthritis Responding Inadequately to Methotrexate

Summary

EudraCT number	2011-002067-20
Trial protocol	DE GB HU PT AT IE CZ ES BG FR IT GR
Global end of trial date	13 January 2016

Results information

Result version number	v1
This version publication date	09 December 2016
First version publication date	09 December 2016

Trial information

Trial identification

Sponsor protocol code	RA0077

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01500278
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	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & 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	17 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To demonstrate the superiority of short-term (Week 12) treatment in Certolizumab pegol (CZP)+ Methotrexate (MTX)-randomized subjects as compared with Adalimumab (ADA)+MTX-randomized subjecs
• To demonstrate the superiority of long-term (Week 104) treatment in CZP+MTX-randomized subjects as compared with ADA+MTX-randomized subjects, with subjects who switch treatment (Week 12 Non-Responders) counted as treatment failures

Protection of trial subjects:

Not applicable.

Background therapy:

All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. The same dosing regimen (dose and route) was maintained from Baseline through Week 52. At Week 52, subjects were allowed to switch regimens (dose and/or route), but had to continue with an MTX dose of 15 to 25mg/week through Week 104 and were not allowed to change the MTX regimen after Week 52. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously. All subjects were responsible for providing their own MTX, consistent with their provision for such at entry.

Other background therapy as permitted in the protocol.

Evidence for comparator:

Adalimumab is a well established anti-TNF.

Actual start date of recruitment	14 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 78
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Czech Republic: 118
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Hungary: 58
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Mexico: 38

Country: Number of subjects enrolled	Poland: 130
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Romania: 52
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 226
Worldwide total number of subjects	915
EEA total number of subjects	603

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)	737
From 65 to 84 years	178
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in December 2011 and concluded in January 2016.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Treatment Group (RTG) that consisted of all subjects randomized into the study.

Period 1

Period 1 title	Week 0 - Week 12
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CZP+MTX (RTG)

Arm description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.
Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Arm type	Experimental
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:

CZP+MTX group: Subcutaneous injections of CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 Responders.
ADA+MTX group: Subcutaneous injections of CZP 400 mg at Week 12, 14 and 16 followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 ADA+MTX Non-Responders.

Arm title	ADA+MTX (RTG)

Arm description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.
Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Arm type	Active 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:

Subjects in group ADA+MTX received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.

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

Dosage and administration details:

ADA+MTX group: Subcutaneous injections of ADA 40mg at Baseline and then every 2 weeks through Week 102 for Week 12 Responders.
CZP+MTX group: Subcutaneous injections of ADA 40mg at Week 12 and every 2 weeks through Week 102 for Week 12 CZP+MTX Non-Responders.

Number of subjects in period 1	CZP+MTX (RTG)	ADA+MTX (RTG)
Started	457	458
Completed	426	428
Not completed	31	30
Prior history of serious disease	1	-
Exclusion criteria not met	1	-
Sponsor decision	1	-
Consent withdrawn by subject	7	2
Patient decision	1	-
Adverse event, non-fatal	7	8
Personal reason	-	1
Investigator decision	1	-
Protocol violation on screening X-ray	1	-
Other serious disease	-	1
Lost to follow-up	1	1
Protocol deviation	10	16
Lack of efficacy	-	1

Period 2

Period 2 title	Week 13 - Week 104
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	CZP+MTX (RTG)

Arm description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.
Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

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

Dosage and administration details:

ADA+MTX group: Subcutaneous injections of ADA 40mg at Baseline and then every 2 weeks through Week 102 for Week 12 Responders.
CZP+MTX group: Subcutaneous injections of ADA 40mg at Week 12 and every 2 weeks through Week 102 for Week 12 CZP+MTX Non-Responders.

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:

CZP+MTX group: Subcutaneous injections of CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 Responders.
ADA+MTX group: Subcutaneous injections of CZP 400 mg at Week 12, 14 and 16 followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 ADA+MTX Non-Responders.

Arm title	ADA+MTX (RTG)

Arm description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.
Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Arm type	Active comparator

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

Dosage and administration details:

ADA+MTX group: Subcutaneous injections of ADA 40mg at Baseline and then every 2 weeks through Week 102 for Week 12 Responders.
CZP+MTX group: Subcutaneous injections of ADA 40mg at Week 12 and every 2 weeks through Week 102 for Week 12 CZP+MTX Non-Responders.

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:

CZP+MTX group: Subcutaneous injections of CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 Responders.
ADA+MTX group: Subcutaneous injections of CZP 400 mg at Week 12, 14 and 16 followed by a maintenance dose of 200 mg every 2 Weeks until week 102 for Week 12 ADA+MTX Non-Responders.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Period 2 of the study (Week 13 – Week 104) was single blinded, as only investigators were blinded, subjects were not.

Number of subjects in period 2	CZP+MTX (RTG)	ADA+MTX (RTG)
Started	426	428
Completed	287	302
Not completed	139	126
Adverse event, serious fatal	2	4
Relocation	-	1
Exclusion criteria not met	1	-
Patient declined Safety Follow Up Visit	1	-
Abnormal questionable chest X-ray	-	2
Medical monitor decision	-	2
Non/bad compliance	7	5
Sponsor decision	-	2
Recurrent infections	1	-
Consent withdrawn by subject	22	13
Withdrawn in error	1	-
Protocol violation	1	-
Adverse event, non-fatal	54	54
Personal reason	-	1
False positive test	1	2
Sponsor request	4	-
Week 24 Non-Responder	20	16

Lost to follow-up	6	5
Principal investigator retiring	1	-
Lack of efficacy	11	12
Protocol deviation	6	6
Not completed	-	1

Baseline characteristics

Reporting groups	
Reporting group title	CZP+MTX (RTG)

Reporting group description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.
Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Reporting group title	ADA+MTX (RTG)

Reporting group description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.
Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Reporting group values	CZP+MTX (RTG)	ADA+MTX (RTG)	Total
Number of subjects	457	458	915
Age Categorical Units: Subjects			
<=18 years	0	1	1
Between 18 and 65 years	364	372	736
>=65 years	93	85	178
Age Continuous Units: years			
arithmetic mean	53.5	52.9	
standard deviation	± 12.3	± 12.8	-
Gender Categorical Units: Subjects			
Male	97	95	192
Female	360	363	723

End points

End points reporting groups

Reporting group title	CZP+MTX (RTG)

Reporting group description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.
Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Reporting group title	ADA+MTX (RTG)

Reporting group description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.
Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Reporting group title	CZP+MTX (RTG)

Reporting group description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.
Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Reporting group title	ADA+MTX (RTG)

Reporting group description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.
Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Subject analysis set title	CZP+MTX (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least 1 dose of Certolizumab pegol (CZP).
All adverse events that occurred when the subject was receiving CZP treatment are summarized in this group.

Subject analysis set title	ADA+MTX (SS)

Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least 1 dose of Adalimumab (ADA).
All adverse events that occurred when the subject was receiving ADA treatment are summarized in this group.

Subject analysis set title	CZP+MTX (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received loading doses of CZP 400mg (200mg/PFS, ie, 2 injections) at Baseline, and Weeks 2 and 4; and CZP 200mg at Weeks 6, 8, and 10.
Week 12 Responders continued CZP 200mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to receive ADA 40mg at Week 12 and every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued ADA treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Subject analysis set title	ADA+MTX (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received ADA 40mg (40mg/PFS, ie, 1 injection) at Baseline and then every 2 weeks through Week 10. In order to preserve the blind (ie, use of 2 injections) until Week 12, subjects received an injection of PBO in addition to ADA at Baseline, and Weeks 2 and 4.
Week 12 Responders continued ADA 40mg at Week 12 and every 2 weeks thereafter through Week 102.
Week 12 Non-Responders were switched to a loading dose of CZP 400mg at Weeks 12, 14, and 16 followed by CZP 200mg every 2 weeks through Week 22. At Week 24, Week 12 Non-Responders who did not have DAS28(ESR) LDA or a DAS28(ESR) change from Week 12 reduction of ≥1.2 discontinued CZP treatment and were withdrawn from the Treatment Period.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Subject analysis set title	CZP+MTX (Week 12 Responder Set)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

CZP 400 mg at Baseline, Week 2 and Week 4, followed by a maintenance dose of 200 mg every 2 Weeks until Week 102.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Subject analysis set title	ADA+MTX (Week 12 Responder Set)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ADA 40 mg at Baseline and then every 2 Weeks until Week 102. Subjects received PBO in addition to ADA at baseline and weeks 2 and 4 in order to maintain the blinding.
All subjects received Methotrexate 15 to 25mg/week orally or subcutaneously from Baseline through Week 104. Regimens could have been changed at Week 52 only. Subjects who could not tolerate these doses could receive MTX at a minimum dose of 10mg/week orally or subcutaneously.

Primary: Percentage of subjects who met the American College of Rheumatology 20 % (ACR20) criteria at Week 12

End point title	Percentage of subjects who met the American College of Rheumatology 20 % (ACR20) criteria at Week 12

End point description:

Subjects who met the ACR20 criteria were those subjects with at least 20% improvement from Baseline for Tender Joint Count (TJC), Swollen Joint Count (SJC), and at least 3 of the 5 remaining core set measures: 1) Health Assessment Questionnaire-Disability Index (HAQ-DI), 2) C-reactive Protein (CRP), 3) Patient's Assessment of Arthritis Pain-Visual Analog Scale (PAAP-VAS), 4) Patient's Global Assessment of Disease Activity-Visual Analog Scale (PtGADA-VAS), 5) Physician's Global Assessment of Disease Activity-Visual Analog Scale (PhGA-VAS).

End point type	Primary

End point timeframe:

Week 12

End point values	CZP+MTX (FAS)	ADA+MTX (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	454		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	69.2	71.4		

Statistical analyses

Statistical analysis title	Odds Ratio for Difference in Responders
Comparison groups	ADA+MTX (FAS) v CZP+MTX (FAS)
Number of subjects included in analysis	908
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.467 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.2

Notes:

[1] - The odds ratio, CI, and p-value are from a logistic regression model with RTG, gender, Baseline duration of RA (<2 years or >=2 years), and geographic region as factors and age as a covariate.

Primary: Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104

End point title	Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104

End point description:

DAS28 [ESR] was 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 Patient Global Assessment of Arthritis, where 28 joints were examined and a lower score indicates less disease activity.

End point type	Primary

End point timeframe:

Week 104

End point values	CZP+MTX (FAS)	ADA+MTX (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	454		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	35.5	33.5		

Statistical analyses

Statistical analysis title	Odds Ratio for Difference in Responders
Comparison groups	CZP+MTX (FAS) v ADA+MTX (FAS)
Number of subjects included in analysis	908
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.532 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.45

Notes:

[2] - The odds ratio, CI and p-value are from a logistic regression model with RTG, gender, Baseline duration of RA (<2 years or >=2 years), and geographic region as factors and Baseline DAS28(ESR) and age as covariates.

Secondary: Percentage of Week 12 responders who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104

End point title	Percentage of Week 12 responders who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104

End point description:

DAS28 [ESR] was 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 Patient Global Assessment of Arthritis, where 28 joints were examined and a lower score indicates less disease activity.
The definition of Week 12 responders was DAS28[ESR] Low Disease Activity (LDA) (ie ≤ 3.2) or an improvement of ≥ 1.2 in DAS28[ESR] relative to Baseline.

End point type	Secondary

End point timeframe:

Week 104

End point values	CZP+MTX (Week 12 Responder Set)	ADA+MTX (Week 12 Responder Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	353	361		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	45.6	42.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who met the American College of Rheumatology 20 % (ACR20) criteria at Week 6

End point title	Percentage of subjects who met the American College of Rheumatology 20 % (ACR20) criteria at Week 6

End point description:

Subjects who met the ACR20 criteria were those subjects with at least 20% improvement from Baseline for Tender Joint Count (TJC), Swollen Joint Count (SJC), and at least 3 of the 5 remaining core set measures: 1) Health Assessment Questionnaire-Disability Index (HAQ-DI), 2) C-reactive Protein (CRP), 3) Patient's Assessment of Arthritis Pain-Visual Analog Scale (PAAP-VAS), 4) Patient's Global Assessment of Disease Activity-Visual Analog Scale (PtGADA-VAS), 5) Physician's Global Assessment of Disease Activity-Visual Analog Scale (PhGA-VAS).

End point type	Secondary

End point timeframe:

Week 6

End point values	CZP+MTX (FAS)	ADA+MTX (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	454		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	64.5	60.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 6

End point title	Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 6

End point description:

DAS28 [ESR] was 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 Patient Global Assessment of Arthritis, where 28 joints were examined and a lower score indicates less disease activity.

End point type	Secondary

End point timeframe:

Week 6

End point values	CZP+MTX (FAS)	ADA+MTX (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	454		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	20.5	18.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 12

End point title	Percentage of subjects who had a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 12

End point description:

DAS28 [ESR] was 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 Patient Global Assessment of Arthritis, where 28 joints were examined and a lower score indicates less disease activity.

End point type	Secondary

End point timeframe:

Week 12

End point values	CZP+MTX (FAS)	ADA+MTX (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	454		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	30.4	29.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104, in subjects responding at both Week 6 and Week 12

End point title	Percentage of subjects with a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 104, in subjects responding at both Week 6 and Week 12

End point description:

DAS28 [ESR] was 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 Patient Global Assessment of Arthritis, where 28 joints were examined and a lower score indicates less disease activity.
The definition of Week 6/12 responders was DAS28[ESR] Low Disease Activity (LDA) (ie ≤ 3.2) or an improvement of ≥ 1.2 in DAS28[ESR] relative to Baseline.

End point type	Secondary

End point timeframe:

Week 104

End point values	CZP+MTX (Week 12 Responder Set)	ADA+MTX (Week 12 Responder Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	310	298		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	47.7	46.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 104

End point title	Change from Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 104

End point description:

HAQ-DI was derived based on the mean of individual scores in 8 categories of daily living actives (using 20 questions). Each question was scored 0-3 (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do). Change from Baseline was computed as the value at Week 104 minus the Baseline value. A negative value in Change from Baseline indicates an improvement.

End point type	Secondary

End point timeframe:

From Baseline to Week 104

End point values	CZP+MTX (FAS)	ADA+MTX (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	454		
Units: least squares mean				
least squares mean (standard error)				
Least squares mean	-0.62 (± 0.03)	-0.72 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to all-cause study discontinuation, defined as the number of days from response at Week 12 until completion at Week 104 or withdrawal before Week 104

End point title	Time to all-cause study discontinuation, defined as the number of days from response at Week 12 until completion at Week 104 or withdrawal before Week 104

End point description:

Response at Week 12 means that a subject had either a Disease Activity Score 28 [Erythrocyte Sedimentation Rate] (DAS28 [ESR]) ≤ 3.2 at Week 12 or had a reduction of DAS28 [ESR] ≥ 1.2 from Baseline to Week 12.
Time to all-cause study discontinuation was defined as the length in days from Week 12 response until completion at Week 104 or until withdrawal before Week 104. Week 12 responders who complete the study will be censored at the Week 104 visit.
Kaplan-Meier Estimates of Proportion Discontinued are presented as results.

End point type	Secondary

End point timeframe:

From Week 12 up to Week 104

End point values	CZP+MTX (Week 12 Responder Set)	ADA+MTX (Week 12 Responder Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	353	361		
Units: proportion of subjects				
number (not applicable)				
Week 13 (Day 7)	0	0.0028		
Week 26 (Day 98)	0.0198	0.0332		
Week 39 (Day 189)	0.0453	0.0609		
Week 52 (Day 280)	0.0963	0.0886		
Week 65 (Day 371)	0.1643	0.1607		
Week 78 (Day 462)	0.2181	0.1967		
Week 91 (Day 553)	0.2408	0.2105		
Week 104 (Day 644)	0.2635	0.2247		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the entire study period (From Week -4 to Week 104).	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	CZP+MTX (SS)
Reporting group description:	
All subjects who received at least 1 dose of Certolizumab pegol (CZP). All adverse events that occurred when the subject was receiving CZP treatment are summarized in this group.	
Reporting group title	ADA+MTX (SS)
Reporting group description:	
All subjects who received at least 1 dose of Adalimumab (ADA). All adverse events that occurred when the subject was receiving ADA treatment are summarized in this group.	

Serious adverse events	CZP+MTX (SS)	ADA+MTX (SS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 516 (12.98%)	58 / 523 (11.09%)	
number of deaths (all causes)	3	3	
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 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 516 (0.19%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 516 (0.19%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Borderline mucinous tumour of ovary			

subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian adenoma			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
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 / 516 (0.19%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis			

subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (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 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (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			
Osteosynthesis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy with contraceptive device			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Impaired healing			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 516 (0.00%)	2 / 523 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
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			
Asthma			

subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 516 (0.39%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			

subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural heamatoma			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	2 / 516 (0.39%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ancle fracture			

subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
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 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			

subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 516 (0.39%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 516 (0.19%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (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	1 / 516 (0.19%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
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	2 / 516 (0.39%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 516 (0.19%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (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 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Ophthalmic vein thrombosis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Obstruction gastric			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal stenosis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal varices			

subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 516 (0.19%)	2 / 523 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 516 (0.00%)	4 / 523 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone disorder			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invertebral disc protrusion			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torticollis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 516 (0.39%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			

subjects affected / exposed	3 / 516 (0.58%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon disorder			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 516 (0.19%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Mycobacterial infection			

subjects affected / exposed	2 / 516 (0.39%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 516 (0.00%)	2 / 523 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oophoritis			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 516 (0.19%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 516 (1.16%)	5 / 523 (0.96%)	
occurrences causally related to treatment / all	2 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 516 (0.19%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated tuberculosis			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 516 (0.39%)	0 / 523 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 516 (0.39%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 516 (0.00%)	1 / 523 (0.19%)	
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	CZP+MTX (SS)	ADA+MTX (SS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	269 / 516 (52.13%)	244 / 523 (46.65%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	37 / 516 (7.17%)	31 / 523 (5.93%)	
occurrences (all)	42	34	
Nervous system disorders			
Headache			
subjects affected / exposed	55 / 516 (10.66%)	47 / 523 (8.99%)	
occurrences (all)	62	77	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	31 / 516 (6.01%)	23 / 523 (4.40%)	
occurrences (all)	36	26	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 516 (4.07%)	28 / 523 (5.35%)	
occurrences (all)	26	35	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	79 / 516 (15.31%)	67 / 523 (12.81%)	
occurrences (all)	116	106	
Upper respiratory tract infection			
subjects affected / exposed	53 / 516 (10.27%)	60 / 523 (11.47%)	
occurrences (all)	74	80	

Urinary tract infection			
subjects affected / exposed	43 / 516 (8.33%)	51 / 523 (9.75%)	
occurrences (all)	58	65	
Latent tuberculosis			
subjects affected / exposed	31 / 516 (6.01%)	27 / 523 (5.16%)	
occurrences (all)	31	27	
Sinusitis			
subjects affected / exposed	31 / 516 (6.01%)	21 / 523 (4.02%)	
occurrences (all)	35	31	
Bronchitis			
subjects affected / exposed	29 / 516 (5.62%)	25 / 523 (4.78%)	
occurrences (all)	33	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2012	The main purpose was to address operational challenges, changes were considered practical, not to carry excess risk to the study subjects, and to have minimal impact on the study outcome. The changes included: •Washout Periods for analgesic and nonbiologic DMARDs were added to clarify subject eligibility. •Upper limit of eligibility for the liver function tests (LFTs) was increased to >1.5 times since many subjects in the targeted population were taking medications that can cause modest elevations in LFTs. RA is also an inflammatory process, whereby subjects may also have modestly elevated LFTs. •The definition of an inadequate response to MTX was revised to align with clinical practice. •Adjustments to MTX doses and oral corticosteroid doses were permitted during the study. •Revisions to the exclusion criterion that listed bacteria/fungal infections, due to false negative rate associated with various serological tests as well as the lack of specificity provided by chest x-rays with respect to granulomatous changes. •Clarification of the definitions of a positive and negative purified protein derivative test, to minimize the risk of missing a subject with possible LTB infection. •Addition of -cotinine level measurement, as a validated marker of exposure to smoking, since smoking exposure is linked to an increase risk of developing RA, and exposure to smoking also impedes the effectiveness of biologic DMARDs. -extra sampling time points for IMP antibody determination and in particular for the genomic analysis were included to allow for early detection of IMP antibodies and genomic biomarkers. •Since prior anti-TNF use was an exclusion criterion, this class of medication was removed as a covariate in the primary efficacy analysis. •Changes were implemented to minimize/eliminate the confounding effect of substance abuse, since recreational drugs frequently can induce expectations or effects that may enhance or mask a disease entity under study such as pain.
19 October 2012	The main purpose of this protocol amendment was to update all procedures related to tuberculosis (TB) detection and monitoring in line with the revised UCB policy. The amended changes also included updates of a number of eligibility criteria, specifically: •Clarification of the required clinical parameters to define moderate to severe RA disease at Screening and Baseline and the duration of the Washout Periods for analgesics and nonbiologic DMARDs. •The upper limit of eligibility for the LFTs was increased to >2.0 times since RA is an inflammatory process that may lead to modestly elevated LFTs and many subjects in the targeted population were taking medications, which can also cause modest elevations in LFTs. Study procedure revisions included: •Any safety laboratory parameter could be repeated when the result was considered erroneous in the judgment of the Investigator or if it was known that the sample could have been mishandled. •The number of sampling times for the genomic analysis was reduced. •The definition of an inadequate response to MTX was revised to emphasize that the decision was based on the Investigator’s clinical judgment.

24 July 2013	The main purpose was to provide further clarification to support interpretation. The clarifications included: •Dose adjustments of oral corticosteroids during the 28 days prior to Baseline were to be avoided unless clinically necessary. The respective language was updated for clarity. Guidelines for discontinuation/tapering of oral corticosteroids permitted during the study were amended with more details •Guidance to ensure an appropriate washout of prior medication was updated for clarity and also specified information regarding the washout of leflunomide •RA-related exclusion criteria were updated with more specific information regarding subjects with systemic lupus erythematosus, lupus nephritis, and Sjogren's Syndrome •Duration of exclusionary periods for subjects with a history of chronic/recurrent infections was decreased to 6 months preceding the study for subjects with more than 3 episodes requiring antibiotics/antivirals and increased to 12 months prior to Baseline for subjects with recent serious/life-hreatening infection •Exclusion criterion related to a history/active systemic/respiratory infection was updated with more details regarding radiographic findings •Guidance for the exclusion of subjects with hepatitis B or C infection including assessments of hepatitis-related biomarkers and for subjects with any positive findings in the urine drug screen •Noncompliance with the protocol-defined visit schedule was a reason for withdrawal. This withdrawal criterion was updated to provide additional guidance •Amendment of inclusion criterions to further emphasize that abstinence was not considered an acceptable method •Addition of albumin and creatinine to the list of clinical chemistry parameters •Update of the -list of the most common adverse reactions in clinical studies of ADA to match the latest version of the ADA SmPC -section describing the handling of protocol deviations to reflect process related changes resulting from the Submission Excellence Program
26 March 2014	The main purposes were: •To clarify the timing of the primary endpoint analyses •To note how unblinding of individual treatment allocation codes were to be handled at the Week 104/WD visit The analysis of data for the Week 12 and Week 104 primary endpoints was changed to be done only at the completion of the study. The reason for this change was that knowledge of the Week 12 efficacy results could bias the way that the Investigators and/or subjects performed assessments or completed the study, which could compromise the interpretation of the final results and/or conclusions. Once all the efficacy assessments were performed for an individual subject at Week 104/WD, the blinded team had the opportunity to unblind the treatment allocation code for that subject. The reason was to aid the Investigator's decision regarding RA treatment after the study. To confirm that this by subject-unblinding did not impact the study results, a sensitivity analysis was added in which all subjects who had their TJC/SJC values at Week 104/WD changed post-visit were excluded. Other changes were: •Modification of text relating to storage and handling of study drugs. •Blood sampling for cotinine at withdrawal did not need to be done if the withdrawal was due to the subject being ineligible to continue in the study at Week 24. •Clarification that all chest radiographs had to be both read and reported by a qualified radiologist. •Addition of text regarding the method of documentation of RA treatment after Week 104/WD. •The ISRQ/SIAQ was performed throughout the study as planned. However, statistical analysis of these questionnaires might not be performed for data at later time points in the study, because the available commercial ADA had undergone an alteration of the needle gauge during this study, which could affect the responses of the subjects to these questionnaires. •Addition of analysis sets needed for selected analyses based on subjects that reached Week 12 and continued in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported