Clinical trial results:
Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Efficacy and Safety of Certolizumab Pegol in Subjects With Active Axial Spondyloarthritis (axSpA) Without X-Ray Evidence of Ankylosing Spondylitis (AS) and Objective Signs of Inflammation

Summary

EudraCT number	2015-001894-41
Trial protocol	HU CZ BG
Global end of trial date	05 May 2020

Results information

Result version number	v1 (current)
This version publication date	16 May 2021
First version publication date	16 May 2021

Trial information

Trial identification

Sponsor protocol code	AS0006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02552212
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES GmbH
Sponsor organisation address	Alfred-Nobel-Strasse 10, Monheim, Germany, 40789
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	09 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2018
Global end of trial reached?	Yes
Global end of trial date	05 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of certolizumab pegol (CZP) 200 mg every 2 weeks (Q2W) on the signs and symptoms of subjects with active Axial Spondyloarthritis (axSpA) without x-ray evidence of Ankylosing Spondylitis (AS).

Protection of trial subjects:

During the conduct of the study all subjects were closely monitored.

Background therapy:

Background therapy as permitted in the protocol

Evidence for comparator:

A Placebo-arm was used to investigate the natural course of the disease compared to the treatment with the Tumor Necrosis Factor (TNF)-inhibitor CZP.

Actual start date of recruitment	03 September 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Bulgaria: 14
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Czechia: 73
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Poland: 112
Country: Number of subjects enrolled	Russian Federation: 55
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	317
EEA total number of subjects	205

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)	314
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll participants in September 2015. The study included a Screening Period, up to 6 weeks before Baseline, a Double-Blind (DB) Period from Baseline (Week 0) to Week 52, that included the open label CZP (OL-CZP) treatment and other treatment (OT) and an Open Label Safety Follow-up Extension (SFE) Period, up to Week 156.

Pre-assignment

Screening details:

The Participant Flow refers to the Randomized Set (RS).

Period 1

Period 1 title	Double-Blind Period (Week 0 - 52)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Assessor, Investigator, Monitor

Blinding implementation details:

Subjects who discontinued the double-blind (DB) study treatment entered the open-label treatment with CZP (OL), or received other treatment (OT) (including biologics).

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo to certolizumab pegol (CZP) injections were administered every 2 weeks from Week 0 onwards.

Arm type	Placebo
Investigational medicinal product name	PLACEBO
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo to certolizumab pegol (CZP) injections were administered every 2 weeks from Week 0 onwards.

Arm title	CZP 200 mg Q2W

Arm description:

Certolizumab pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.

Arm type	Experimental
Investigational medicinal product name	CERTOLIZUMAB PEGOL
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Certolizumab pegol (CZP) 400 mg subcutaneous (sc) on Week 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.

Number of subjects in period 1	Placebo	CZP 200 mg Q2W
Started	158	159
Received OL CZP	96 [1]	20 [2]
Completed Week 52 without starting SFE	20 [3]	22 [4]
Completed	143	142
Not completed	15	17
Consent withdrawn by subject	3	7
Not eligible	-	1
Adverse event, non-fatal	6	3
As per suggestion	-	1
Patient's decision	-	1
Study non-compliance	1	1
Lost to follow-up	1	-
Missing/Unspecified	1	-
Lack of efficacy	2	2
Protocol deviation	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who received OL CZP during the Double-Blind Period (Week 0 -52).

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who received OL CZP during the Double-Blind Period (Week 0 -52).

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who completed the Week 52 and did not sign the informed consent form for entering the SFE Period.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at this milestone reflect those who completed the Week 52 and did not sign the informed consent form for entering the SFE Period.

Period 2

Period 2 title	SFE Period (Week 52 - 156)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	SFE OL CZP 200 mg Q2W

Arm description:

Subjects who completed Double-Blind Period received CZP 200 mg at Week 52, 54 and 56 to maintain the blinding and who completed the Week 52 Visit on placebo treatment received loading doses of CZP 400 mg at these visits. Subjects who completed the Week 52 Visit on CZP treatment received 1 injection of CZP 200 mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen and subjects who discontinued from Double-Blind Period and entered OL CZP treatment continued their OL CZP treatment regimen during Safety Follow-Up Extension (SFE) Period. Subjects received CZP 200 mg Q2W for up to 2 years during the SFE Period. An additional signed informed consent for the SFE was a pre-requisite For the additional milestone one (Received OL CZP; Completed Week 52 without starting SFE) reported in Double-Blind Period (Week 0 - 52).

Arm type	Experimental
Investigational medicinal product name	CERTOLIZUMAB PEGOL
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Certolizumab pegol (CZP) 400 mg subcutaneous (sc) on Week 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.

Number of subjects in period 2[5]	SFE OL CZP 200 mg Q2W
Started	243
Completed	206
Not completed	37
Consent withdrawn by subject	18
Patient's personal reason	1
Adverse event, non-fatal	5
Subject withdrew consent due to traveling to site	1
Patient travelling for study unable to continue	1
Investigator decision	1
Compassionate access	2
Return to standard-of-care /OL CZP	1
Lost to follow-up	2
Decision of Patient	1
Lack of efficacy	4

Notes:

[5] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 285 study participants completed the Double-Blind Period (Week 52). 42 study participants, 20 on placebo and 22 on Cimzia 200 mg Q2W, did not sign the additional informed consent required for the SFE Period. Only 243 study participants started the SFE Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to certolizumab pegol (CZP) injections were administered every 2 weeks from Week 0 onwards.	
Reporting group title	CZP 200 mg Q2W
Reporting group description:	
Certolizumab pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.	

Reporting group values	Placebo	CZP 200 mg Q2W	Total
Number of subjects	158	159	317
Age categorical			
Units: Subjects			
<=18 years	3	1	4
Between 18 and 65 years	154	156	310
>=65 years	1	2	3
Age continuous			
Units: years			
arithmetic mean	37.4	37.3	
standard deviation	± 10.8	± 10.5	-
Gender categorical			
Units: Subjects			
Female	82	81	163
Male	76	78	154

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Matching placebo to certolizumab pegol (CZP) injections were administered every 2 weeks from Week 0 onwards.

Reporting group title	CZP 200 mg Q2W

Reporting group description:

Certolizumab pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.

Reporting group title	SFE OL CZP 200 mg Q2W

Reporting group description:

Subjects who completed Double-Blind Period received CZP 200 mg at Week 52, 54 and 56 to maintain the blinding and who completed the Week 52 Visit on placebo treatment received loading doses of CZP 400 mg at these visits. Subjects who completed the Week 52 Visit on CZP treatment received 1 injection of CZP 200 mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen and subjects who discontinued from Double-Blind Period and entered OL CZP treatment continued their OL CZP treatment regimen during Safety Follow-Up Extension (SFE) Period. Subjects received CZP 200 mg Q2W for up to 2 years during the SFE Period. An additional signed informed consent for the SFE was a pre-requisite For the additional milestone one (Received OL CZP; Completed Week 52 without starting SFE) reported in Double-Blind Period (Week 0 - 52).

Subject analysis set title	Placebo (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Matching placebo to certolizumab pegol (CZP) injections were administered every 2 weeks from Week 0 onwards. Subjects formed the Safety Set (SS).

Subject analysis set title	CZP 200 mg Q2W (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Certolizumab pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards. Subjects formed the SS.

Subject analysis set title	Placebo->OL CZP (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subset of subjects from the Placebo group, who discontinued the CZP double-blind treatment and entered the open-label CZP treatment. The subjects were included in the SS for safety analysis.

Subject analysis set title	CZP->OL CZP (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subset of subjects from the CZP 200 mg Q2W group, who discontinued the CZP double-blind treatment and entered the CZP open-label treatment. The subjects were included in the SS for safety analysis.

Subject analysis set title	SFE OL CZP 200 mg Q2W (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who completed Double-Blind Period received CZP 200 mg at Week 52, 54 and 56 to maintain the blinding and who completed the Week 52 Visit on placebo treatment received loading doses of CZP 400 mg at these visits. Subjects who completed the Week 52 Visit on CZP treatment received 1 injection of CZP 200 mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen and subjects who discontinued from Double-Blind Period and entered OL CZP treatment continued their OL CZP treatment regimen during SFE Period. The subjects were included in the SS for safety analysis. Subjects received CZP 200 mg Q2W for up to 2 years during the SFE Period. An additional signed informed consent for the SFE was a pre-requisite For the additional milestone one (Received OL CZP; Completed Week 52 without starting SFE) reported in Double-Blind Period (Week 0 - 52).

Subject analysis set title	Placebo (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Matching placebo to certolizumab pegol (CZP) injections were administered every 2 weeks from Week 0 onwards. Subjects formed the Full Analysis Set (FAS).

Subject analysis set title	CZP 200 mg Q2W (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Certolizumab pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards. Subjects formed the FAS.

Subject analysis set title	SFE OL CZP 200 mg Q2W (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed Double-Blind Period received CZP 200 mg at Week 52, 54 and 56 to maintain the blinding and who completed the Week 52 Visit on placebo treatment received loading doses of CZP 400 mg at these visits. Subjects who completed the Week 52 Visit on CZP treatment received 1 injection of CZP 200 mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen and subjects who discontinued from Double-Blind Period and entered OL CZP treatment continued their OL CZP treatment regimen during SFE Period. Subjects formed the FAS. Subjects received CZP 200 mg Q2W for up to 2 years during the SFE Period. An additional signed informed consent for the SFE was a pre-requisite For the additional milestone one (Received OL CZP; Completed Week 52 without starting SFE) reported in Double-Blind Period (Week 0 - 52).

Primary: Percentage of subjects with Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response criteria response at Week 52

End point title	Percentage of subjects with Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response criteria response at Week 52

End point description:

This variable was considered as primary in all countries except for Canada (and any other country where applicable or where requested by Regulatory Authorities) where it was considered as secondary variable. ASDAS-MI was achieved when there was a reduction (improvement) >= 2.0 in the ASDAS relative to Baseline, or when the lowest possible ASDAS score (0.6) was reached.
The ASDAS was calculated as the sum of the following components:
0.121 × Back pain (BASDAI Q2 result)
0.058 × Duration of morning stiffness (BASDAI Q6 result)
0.110 × Patient’s Global Assessment of Disease Activity (PGADA)
0.073 × Peripheral pain/swelling (BASDAI Q3 result)
0.579 × (natural logarithm [ln] of the (CRP [mg/L] + 1))
Back pain, PGADA, duration of morning stiffness, peripheral pain/swelling and fatigue were all assessed on a numerical scale (0 to 10 units, where 0 is “not active” and 10 is “very active”). The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Week 52

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: percentage of subjects				
number (not applicable)	7.0	47.2		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Odds ratio: CZP/Placebo and p-value were calculated using logistic regression with factors for treatment, region and Magnetic Resonance Imaging/C- Reactive Protein (MRI/CRP) classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	15.231
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.336
upper limit	31.623

Primary: Percentage of subjects with Axial SpondyloArthritis international Society 40% response criteria (ASAS40) response at Week 12

End point title	Percentage of subjects with Axial SpondyloArthritis international Society 40% response criteria (ASAS40) response at Week 12

End point description:

This variable was considered as primary for Canada (and any other country where applicable or where requested by Regulatory Authorities) and as secondary variable in all other countries.
The ASAS40 response was defined as relative improvements of at least 40 % and absolute improvement of at least 2 units on a 0 to 10 Numeric Rating Scale (NRS), where 0 is “not active” and 10 is “very active” in at least 3 of the 4 domains: Patient's Global Assessment of Disease Activity (PGADA), Pain assessment (total spinal pain NRS scores), Function (Bath Ankylosing Spondylitis Functional Index (BASFI), Inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)) questions 5 and 6 concerning morning stiffness intensity and duration) and no worsening at all in the remaining domain. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: percentage of subjects				
number (not applicable)	11.4	47.8		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Odds ratio: CZP/Placebo and p-value were calculated using logistic regression with factors for treatment, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.436
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.127
upper limit	13.401

Primary: Certolizumab pegol plasma concentration at Baseline

End point title	Certolizumab pegol plasma concentration at Baseline[1]

End point description:

Certolizumab pegol plasma concentration was measured at Baseline in micrograms per millilitre (µg/mL). The Safety Set (SS) consisted of all subjects who have received at least 1 dose of study medication. Note: None of the Safety Set subjects had Pharmacokinetic (PK) concentrations above the lower limit of quantification.

End point type	Primary

End point timeframe:

Baseline (Week 0)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	Placebo (SS)	CZP 200 mg Q2W (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[2]	0[3]		
Units: µg/mL				
geometric mean (confidence interval 95%)	(to)	(to)		

Notes:

[2] - Pharmacokinetic (PK) concentrations were below the lower limit of quantification.

[3] - Pharmacokinetic (PK) concentrations were below the lower limit of quantification.

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab pegol plasma concentration at Week 1

End point title	Certolizumab pegol plasma concentration at Week 1[4]

End point description:

Certolizumab pegol plasma concentration was measured at Week 1, in µg/mL. The SS consisted of all subjects who received at least 1 dose of study treatment. Note: No samples taken at Week 1 for the Placebo->OL CZP.

End point type	Primary

End point timeframe:

Week 1

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	0[5]		
Units: µg/mL				
geometric mean (confidence interval 95%)	50.5 (48.0 to 53.0)	(to)		

Notes:

[5] - No samples taken at Week 1 for the Placebo->OL CZP.

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab pegol plasma concentration at Week 2

End point title	Certolizumab pegol plasma concentration at Week 2[6]

End point description:

Certolizumab pegol plasma concentration was measured at Week 2, in µg/mL. The SS consisted of all subjects who received at least 1 dose of study treatment. Note: No samples taken at Week 2 for the Placebo->OL CZP.

End point type	Primary

End point timeframe:

Week 2

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	153	0[7]		
Units: µg/mL				
geometric mean (confidence interval 95%)	36.4 (33.0 to 40.1)	(to)		

Notes:

[7] - No samples taken at Week 2 for the Placebo->OL CZP.

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab pegol plasma concentration at Week 4

End point title	Certolizumab pegol plasma concentration at Week 4[8]

End point description:

Certolizumab pegol plasma concentration was measured at Week 4, in µg/mL. The SS consisted of all subjects who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

Week 4

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	155	93		
Units: µg/mL				
geometric mean (confidence interval 95%)	54.6 (51.4 to 58.0)	48.8 (42.2 to 56.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab pegol plasma concentration at Week 12

End point title	Certolizumab pegol plasma concentration at Week 12[9]

End point description:

Certolizumab pegol plasma concentration was measured at Week 12, in µg/mL. The SS consisted of all subjects who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

Week 12

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	143	93		
Units: µg/mL				
geometric mean (confidence interval 95%)	29.1 (24.0 to 35.2)	30.5 (26.4 to 35.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab pegol plasma concentration at Week 24

End point title	Certolizumab pegol plasma concentration at Week 24[10]

End point description:

Certolizumab pegol plasma concentration was measured at Week 24, in µg/mL. The SS consisted of all subjects who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

Week 24

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	135	86		
Units: µg/mL				
geometric mean (confidence interval 95%)	23.5 (18.5 to 29.7)	24.8 (20.6 to 29.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab pegol plasma concentration at Week 36

End point title	Certolizumab pegol plasma concentration at Week 36[11]

End point description:

Certolizumab pegol plasma concentration was measured at Week 36, in µg/mL. The SS consisted of all subjects who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

Week 36

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	65		
Units: µg/mL				
geometric mean (confidence interval 95%)	24.0 (19.0 to 30.4)	22.9 (18.3 to 28.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab pegol plasma concentration at Week 52

End point title	Certolizumab pegol plasma concentration at Week 52[12]

End point description:

Certolizumab pegol plasma concentration was measured at Week 52, in µg/mL. The SS consisted of all subjects who received at least 1 dose of study treatment. Note: No samples taken at OL Week 52 for the Placebo->OL CZP.

End point type	Primary

End point timeframe:

Week 52

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	0[13]		
Units: µg/mL				
geometric mean (confidence interval 95%)	22.6 (17.8 to 28.6)	(to)		

Notes:

[13] - No samples taken at OL Week 52 for the Placebo->OL CZP.

Statistical analyses

No statistical analyses for this end point

Primary: Certolizumab pegol plasma concentration at Follow-Up (FU) Visit

End point title	Certolizumab pegol plasma concentration at Follow-Up (FU) Visit[14]

End point description:

Certolizumab pegol plasma concentration was measured at the Follow-Up Visit, in µg/mL.
Follow-Up Visit was defined as 8 weeks after Week 52 or Withdrawal (WD) visit for subjects not participating in the Safety Follow-Up Extension (SFE) Period. The SS consisted of all subjects who received at least 1 dose of study treatment. Only participants included, who had a SFU Visit at 8 weeks after Week 52/WD visit for those not participating in the SFE period.

End point type	Primary

End point timeframe:

Follow-up Visit (up to Week 60)

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

End point values	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	10		
Units: µg/mL				
geometric mean (confidence interval 95%)	0.2 (0.1 to 0.7)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Axial SpondyloArthritis international Society 40% response criteria (ASAS40) response at Week 52

End point title	Percentage of subjects with Axial SpondyloArthritis international Society 40% response criteria (ASAS40) response at Week 52

End point description:

The ASAS40 response was defined as relative improvements of at least 40% and absolute improvement of at least 2 units on a 0 to 10 Numeric Rating Scale (NRS), where 0 is "not active" and 10 is "very active" in at least 3 of the 4 domains: Patient's Global Assessment of Disease Activity (PGADA), Pain assessment (total spinal pain NRS scores), Function (Bath Ankylosing Spondylitis Functional Index (BASFI)), Inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)) questions 5 and 6 concerning morning stiffness intensity and duration) and no worsening at all in the remaining domain. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: percentage of subjects				
number (not applicable)	15.8	56.6		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Odds ratio: CZP/Placebo and p-value were calculated using logistic regression with factors for treatment, region MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.359
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.286
upper limit	12.636

Secondary: Change from Baseline to Week 12 in the Bath Ankylosing Spondylitis Functional Index (BASFI)

End point title	Change from Baseline to Week 12 in the Bath Ankylosing Spondylitis Functional Index (BASFI)

End point description:

The BASFI is a validated disease-specific instrument for assessing physical function. The BASFI comprises 10 items relating to the past week. The BASFI is the mean of the 10 scores such that the total score ranges from 0 (Easy) to 10 (Impossible), with lower scores indicating better physical function. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: scores on a scale				
least squares mean (standard error)	-0.38 (± 0.21)	-2.07 (± 0.20)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

From an ANCOVA model including scores at Baseline, treatment group, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference
Point estimate	-1.696
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	-1.282

Secondary: Change from Baseline to Week 52 in the Bath Ankylosing Spondylitis Functional Index (BASFI)

End point title	Change from Baseline to Week 52 in the Bath Ankylosing Spondylitis Functional Index (BASFI)

End point description:

The BASFI is a validated disease-specific instrument for assessing physical function. The BASFI comprises 10 items relating to the past week. The BASFI is the mean of the 10 scores such that the total score ranges from 0 (Easy) to 10 (Impossible), with lower scores indicating better physical function. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: scores on a scale				
least squares mean (standard error)	-1.44 (± 0.30)	-3.03 (± 0.24)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

From an ANCOVA model including scores at Baseline, treatment group, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference
Point estimate	-1.585
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.132
upper limit	-1.038

Secondary: Change from Baseline to Week 12 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

End point title	Change from Baseline to Week 12 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

End point description:

The BASDAI is a validated self-reported instrument, which consists of six 10 unit horizontal Numeric Rating Scales to measure the disease activity of ankylosing spondylitis (AS) from the subject's perspective. It measures the severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration) over the last week. The final BASDAI scores ranges from 0 (not active) to 10 (very active), with lower scores indicating lower disease activity. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: scores on a scale				
least squares mean (standard error)	-0.91 (± 0.22)	-2.73 (± 0.21)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

From an ANCOVA model including scores at Baseline, treatment group, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference
Point estimate	-1.819
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.25
upper limit	-1.388

Secondary: Change from Baseline to Week 52 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

End point title	Change from Baseline to Week 52 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

End point description:

The BASDAI is a validated self-reported instrument, which consists of six 10 unit horizontal Numeric Rating Scales to measure the disease activity of ankylosing spondylitis (AS) from the subject's perspective. It measures the severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration) over the last week. The final BASDAI scores ranges from 0 (not active) to 10 (very active), with lower scores indicating lower disease activity. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: scores on a scale				
least squares mean (standard error)	-2.59 (± 0.37)	-3.88 (± 0.27)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

From an ANCOVA model including scores at Baseline, treatment group, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.909
upper limit	-0.672

Secondary: Change from Baseline to Week 12 in sacroiliac Spondyloarthritis Research Consortium of Canada (SI-SPARCC) score

End point title	Change from Baseline to Week 12 in sacroiliac Spondyloarthritis Research Consortium of Canada (SI-SPARCC) score

End point description:

The Spondyloarthritis Research Consortium of Canada (SPARCC) scoring method for lesions found on the Magnetic Resonance Imaging (MRI) is based on an abnormal increased signal on the Short-Tau-Inversion Recovery (STIR) sequence, representing bone marrow edema. Total Sacroiliac (SI) joint SPARCC score can range from 0 to 72 with higher scores indicating higher joint inflammation. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: scores on a scale				
least squares mean (standard error)	0.200 (± 0.772)	-4.669 (± 0.770)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

From an ANCOVA model including scores at Baseline, treatment group, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference
Point estimate	-4.8687
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4014
upper limit	-3.336

Secondary: Number of subjects without relevant changes to background medication from Baseline to Week 52

End point title	Number of subjects without relevant changes to background medication from Baseline to Week 52

End point description:

The number of subjects who did not have relevant changes to background medications during the study treatment period.
A subject is without relevant changes to background medication if they do not have: the addition of a new disease-modifying antirheumatic drug (DMARD) or the change from one DMAR to another; the addition of an nonsteroidal anti-inflammatory drug (NSAID) or the change from one NSAID to another; an increased dose of chronic corticosteroids; the addition of a new chronic analgesic medication or increased dose in chronic analgesic medication; and they complete double-blind study treatment to Week 52. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: participants	48	115		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Odds ratio: CZP/Placebo and p-value were calculated using logistic regression with factors for treatment, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.223
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	10.191

Secondary: Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) at Week 52

End point title	Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) at Week 52

End point description:

The ASQoL score ranged from 0 to 18 with higher score indicating worse Health-Related Quality of Life (HRQoL) and 0 indicating good HRQoL. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: scores on a scale				
least squares mean (standard error)	-0.18 (± 0.04)	-0.36 (± 0.03)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

From an ANCOVA model including scores at Baseline, teratment group, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)

Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference
Point estimate	-0.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	-0.117

Secondary: Change from Baseline in ASQoL at Week 1

End point title	Change from Baseline in ASQoL at Week 1

End point description:

The ASQoL score ranged from 0 to 18 with higher score indicating worse Health-Related Quality of Life (HRQoL) and 0 indicating good HRQoL. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 1

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150	147		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.03 (± 0.14)	-0.11 (± 0.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ASQoL at Week 2

End point title	Change from Baseline in ASQoL at Week 2

End point description:

The ASQoL score ranged from 0 to 18 with higher score indicating worse Health-Related Quality of Life (HRQoL) and 0 indicating good HRQoL. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 2

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	156		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.03 (± 0.15)	-0.16 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ASQoL at Week 4

End point title	Change from Baseline in ASQoL at Week 4

End point description:

The ASQoL score ranged from 0 to 18 with higher score indicating worse Health-Related Quality of Life (HRQoL) and 0 indicating good HRQoL. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 4

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	156		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.06 (± 0.19)	-0.18 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ASQoL at Week 12

End point title	Change from Baseline in ASQoL at Week 12

End point description:

The ASQoL score ranged from 0 to 18 with higher score indicating worse Health-Related Quality of Life (HRQoL) and 0 indicating good HRQoL. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	156		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.08 (± 0.22)	-0.28 (± 0.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ASQoL at Week 24

End point title	Change from Baseline in ASQoL at Week 24

End point description:

The ASQoL score ranged from 0 to 18 with higher score indicating worse Health-Related Quality of Life (HRQoL) and 0 indicating good HRQoL. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	156		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.09 (± 0.23)	-0.31 (± 0.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ASQoL at Week 36

End point title	Change from Baseline in ASQoL at Week 36

End point description:

The ASQoL score ranged from 0 to 18 with higher score indicating worse Health-Related Quality of Life (HRQoL) and 0 indicating good HRQoL. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 36

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	156		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.11 (± 0.23)	-0.33 (± 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ASQoL at Week 48

End point title	Change from Baseline in ASQoL at Week 48

End point description:

The ASQoL score ranged from 0 to 18 with higher score indicating worse Health-Related Quality of Life (HRQoL) and 0 indicating good HRQoL. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 48

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	156		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.10 (± 0.24)	-0.34 (± 0.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in nocturnal spinal pain Numerical Rating Scale (NRS) at Week 52

End point title	Change from Baseline in nocturnal spinal pain Numerical Rating Scale (NRS) at Week 52

End point description:

The nocturnal spinal pain experienced by subjects due to AS was measured by following question 'How

much pain of your spine due to spondylitis do you have at night?'. The NRS ranged from 0 to 10, where 0 represented 'no pain' and 10 represented 'most severe pain'. The change from Baseline is calculated, a negative value indicating improvement and a positive value worsening. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: scores on a scale				
least squares mean (standard error)	-2.1 (± 0.5)	-4.0 (± 0.4)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

From an ANCOVA model including scores at Baseline, treatment group, region and MRI/CRP classification.

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.62
upper limit	-1.18

Secondary: Number of subjects with anterior uveitis (AU) or new AU flares through Week 52

End point title	Number of subjects with anterior uveitis (AU) or new AU flares through Week 52

End point description:

The number of subjects with AU or new AU flares during the study treatment period. The FAS consisted of all subjects in the RS who have received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Throughout the study conduct (up to Week 52)

End point values	Placebo (FAS)	CZP 200 mg Q2W (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	159		
Units: participants	8	4		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Odds ratio: CZP/PBO and p-value were calculated using logistic regression with factors for treatment, region and MRI/CRP classification.	
Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.247
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.484
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.142
upper limit	1.653

Secondary: Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs) During the Study

End point title	Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs) During the Study
End point description:	
An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The SS consisted of all subjects who received at least 1 dose of study treatment.	
End point type	Secondary
End point timeframe:	
From Baseline up to the End of Safety Follow-up Extenision Period (up to Week 156)	

End point values	Placebo (SS)	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)	CZP->OL CZP (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	158	159	96	20
Units: percentage of subjects				
number (not applicable)	63.9	75.5	59.4	65.0

End point values	SFE OL CZP 200 mg Q2W (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	243			
Units: percentage of subjects				
number (not applicable)	61.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Serious Adverse Events (SAEs) During the Study

End point title	Percentage of Subjects with Serious Adverse Events (SAEs) During the Study

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening
- Requires in patient hospitalization or prolongation of existing hospitalization
- Is a congenital anomaly or birth defect
- Is an infection that requires treatment parenteral antibiotics
- Other important medical events which based on medical or scientific judgement may jeopardize the patients, or may require medical or surgical intervention to prevent any of the above. The SS consisted of all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From Baseline up to the End of Safety Follow-up Extenision Period (up to Week 156)

End point values	Placebo (SS)	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)	CZP->OL CZP (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	158	159	96	20
Units: percentage of subjects				
number (not applicable)	2.5	5.0	3.1	5.0

End point values	SFE OL CZP			

	200 mg Q2W (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	243			
Units: percentage of subjects				
number (not applicable)	6.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events Leading to Withdrawal from Investigational Medicinal Product (IMP) During the Study

End point title	Percentage of Subjects with Adverse Events Leading to Withdrawal from Investigational Medicinal Product (IMP) During the Study

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The SS consisted of all subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From Baseline up to the End of Safety Follow-up Extenision Period (up to Week 156)

End point values	Placebo (SS)	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)	CZP->OL CZP (SS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	158	159	96	20
Units: percentage of subjects				
number (not applicable)	1.9	1.9	3.1	0

End point values	SFE OL CZP 200 mg Q2W (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	243			
Units: percentage of subjects				
number (not applicable)	2.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to the End of Safety Follow-up Extenision Period (up to Week 156)

Adverse event reporting additional description:

Adverse events were recorded for all subjects, including those who discontinued the blinded treatment and entered the open-label treatment with CZP (OL). Based on this the following groups were generated: Placebo, Placebo-> OL CZP, CZP, CZP->OL CZP and OL CZP during SFE Period for all subjects entering the SFE Period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo (SS)

Reporting group description:

Matching placebo to certolizumab pegol (CZP) injections were administered every 2 weeks from Week 0 onwards. Subjects formed the Safety Set (SS).

Reporting group title	CZP 200 mg Q2W (SS)

Reporting group description:

Certolizumab pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards. Subjects formed the SS.

Reporting group title	Placebo->OL CZP (SS)

Reporting group description:

Subset of subjects from the Placebo group, who discontinued the CZP double-blind treatment and entered the open-label CZP treatment. The subjects were included in the SS for safety analysis.

Reporting group title	CZP->OL CZP (SS)

Reporting group description:

Subset of subjects from the CZP 200 mg Q2W group, who discontinued the CZP double-blind treatment and entered the CZP open-label treatment. The subjects were included in the SS for safety analysis.

Reporting group title	SFE OL CZP 200 mg Q2W (SS)

Reporting group description:

Subjects who completed Double-Blind Period received CZP 200 mg at Week 52, 54 and 56 to maintain the blinding and who completed the Week 52 Visit on placebo treatment received loading doses of CZP 400 mg at these visits. Subjects who completed the Week 52 Visit on CZP treatment received 1 injection of CZP 200 mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen and subjects who discontinued from Double-Blind Period and entered OL CZP treatment continued their OL CZP treatment regimen during SFE Period. The subjects were included in the SS for safety analysis. Subjects received CZP 200 mg Q2W for up to 2 years during the SFE Period. An additional signed informed consent for the SFE was a pre-requisite For the additional milestone one (Received OL CZP; Completed Week 52 without starting SFE) reported in Double-Blind Period (Week 0 - 52).

Serious adverse events	Placebo (SS)	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 158 (2.53%)	8 / 159 (5.03%)	3 / 96 (3.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Malignant melanoma stage I			
subjects affected / exposed	1 / 158 (0.63%)	0 / 159 (0.00%)	0 / 96 (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
Uterine leiomyoma			
subjects affected / exposed	1 / 158 (0.63%)	0 / 159 (0.00%)	0 / 96 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Hypertension			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Tooth extraction			
subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	1 / 158 (0.63%)	0 / 159 (0.00%)	0 / 96 (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
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 159 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervix neoplasms			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Ovarian cyst ruptured			
subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Hydrosalpinx			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian enlargement			
subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Respiratory, thoracic and mediastinal disorders			
Pharyngeal oedema			

subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Iridocyclitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Uveitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Diarrhoea			
subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Constipation			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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

Gastrointestinal obstruction			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Inguinal hernia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Hypersensitivity vasculitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	1 / 96 (1.04%)
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			
Spinal pain			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Rotator cuff syndrome			

subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Neuroborreliosis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 159 (0.63%)	0 / 96 (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
Encephalitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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 rotavirus			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Tuberculosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Chronic tonsillitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 158 (0.00%)	0 / 159 (0.00%)	0 / 96 (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

Serious adverse events	CZP->OL CZP (SS)	SFE OL CZP 200 mg Q2W (SS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	15 / 243 (6.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from	0	0	

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage I			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth extraction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervix neoplasms			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical polyp			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst ruptured			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrosalpinx			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian enlargement			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pharyngeal oedema			

subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iridocyclitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal obstruction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity vasculitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			

subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neuroborreliosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 243 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 243 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo (SS)	CZP 200 mg Q2W (SS)	Placebo->OL CZP (SS)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 158 (37.34%)	75 / 159 (47.17%)	27 / 96 (28.13%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 158 (2.53%)	8 / 159 (5.03%)	1 / 96 (1.04%)
occurrences (all)	4	9	1
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 158 (4.43%)	11 / 159 (6.92%)	0 / 96 (0.00%)
occurrences (all)	9	15	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 158 (6.33%)	8 / 159 (5.03%)	1 / 96 (1.04%)
occurrences (all)	10	11	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 158 (5.06%)	6 / 159 (3.77%)	2 / 96 (2.08%)
occurrences (all)	10	6	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 158 (6.33%)	9 / 159 (5.66%)	2 / 96 (2.08%)
occurrences (all)	12	12	2
Axial spondyloarthritis			
subjects affected / exposed	12 / 158 (7.59%)	11 / 159 (6.92%)	0 / 96 (0.00%)
occurrences (all)	13	13	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	16 / 158 (10.13%)	30 / 159 (18.87%)	10 / 96 (10.42%)
occurrences (all)	23	38	14
Nasopharyngitis			
subjects affected / exposed	13 / 158 (8.23%)	21 / 159 (13.21%)	10 / 96 (10.42%)
occurrences (all)	17	24	13
Bronchitis			
subjects affected / exposed	5 / 158 (3.16%)	8 / 159 (5.03%)	5 / 96 (5.21%)
occurrences (all)	5	9	5

Non-serious adverse events	CZP->OL CZP (SS)	SFE OL CZP 200 mg Q2W (SS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 20 (35.00%)	69 / 243 (28.40%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 20 (5.00%)	3 / 243 (1.23%)	
occurrences (all)	1	3	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 20 (15.00%)	9 / 243 (3.70%)	
occurrences (all)	3	11	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	4 / 243 (1.65%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 20 (0.00%)	3 / 243 (1.23%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 20 (10.00%)	6 / 243 (2.47%)	
occurrences (all)	2	6	
Axial spondyloarthritis			
subjects affected / exposed	0 / 20 (0.00%)	5 / 243 (2.06%)	
occurrences (all)	0	5	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 20 (20.00%)	21 / 243 (8.64%)	
occurrences (all)	5	31	
Nasopharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	26 / 243 (10.70%)	
occurrences (all)	0	33	
Bronchitis			

subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	10 / 243 (4.12%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2015	Global Protocol Amendment 1 (15 Dec 2015) was implemented to clarify and/or add supporting information regarding the procedures and assessments, and to remove inconsistencies and errors: a range of sensitivity analyses, previously discussed with the regulatory authorities, to evaluate the impact of missing data on the analysis of the primary efficacy variable were added. Other changes included the following: the exclusion criterion regarding the upper limit of normal (ULN) of the liver function tests for subjects who were not treated with methotrexate (MTX), the requirement for plasma samples to be analyzed to confirm the washout of specific prohibited medications was removed, and the reporting-needs of particular physician completed assessments in the electronic Case Report Form (eCRF) were clarified. Two tables were included to assist the Investigators in identifying the assessments to be performed when subjects switched to alternative treatments. Inconsistencies in the laboratory assessments performed, the definition of study treatment, and the use of Week 52 and Week 52/Withdrawal (WD) Visit were corrected, study personal information was updated, and minor editorial changes were made.
14 March 2016	Global Protocol Amendment 2 (14 Mar 2016) was implemented to clarify some of the study procedures, as well as to update Inclusion Criteria 5 and 6 concerning the ASAS criteria, and to increase the number of participating sites and screened subjects. The rationale for the changes was as follows: -Inclusion Criterion 5 about subjects having a documented diagnosis of adult-onset axSpA as defined by the specified ASAS criteria was updated in order to: (i.) clarify that the ASAS criteria were classification criteria and were not intended to be used as diagnosis criteria and to avoid any misinterpretation, and (ii.) removed the part "with at least 12 months symptom duration before Screening," since this part was added to the updated Inclusion Criterion. -Inclusion Criterion 6 about subjects having evidence of inflammatory back pain as defined by the ASAS criteria was updated to specify that subjects must have had back pain for at least 12 months before Screening. The reason was that the requirements for objective signs and symptoms of inflammation were clearly defined in Inclusion Criterion 9. The initial Inclusion Criterion 6 was therefore a repetition of this requirement. The updated version stressed the importance of having back pain as the lead symptom for axSpA for at least 12 months, to ensure that the pain was chronic in nature. -The number of participating sites and the number of screened subjects was increased from 95 to 120 and from 900 to 1200, respectively, in order to adjust for a higher screening failure rate, which was actually exceeding the expected rate of 67%.

13 February 2017	Global Protocol Amendment 3 (13 Feb 2017) was implemented to clarify the study details regarding the additional 2 years of long-term, Open-Label certolizumab pegol (OL-CZP) treatment that was to be provided to eligible subjects at the completion of the Week 52 visit. This period of the study was named the SFE Period and the protocol was updated throughout accordingly (eg, a new Schedule of Study Assessments was added and eligibility criteria, guidance for study treatment administration, and concomitant medication usage were updated). Additional changes included: -Allowing female subjects who became pregnant while participating in the AS0006 study the option to enroll in a separate, observational, pregnancy follow-up study sponsored by UCB. -Removal of the 40% cap on interactive response system (IXRS) randomization to each of the 3 clinical subgroups for magnetic resonance imaging/C-reactive protein (MRI/CRP) classifications: (MRI+/CRP+, MRI+/CRP-, or MRI-/CRP+) in order to reflect the real world situation. -Clarification that cases of potential Hy's Law, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality, were ALWAYS to be reported to UCB as an adverse event (AE) of interest (ie, without waiting for any additional etiologic investigations to have been concluded). -Minor typographical errors were corrected throughout the protocol.
19 December 2017	Global Protocol Amendment 4 (19 Dec 2017) was implemented to add an alternative primary efficacy variable for Canada and any other country where applicable or where requested by Regulatory Authorities. In response to feedback from the Canadian Health Authorities, the primary efficacy variable for Canada (and any other country where applicable or where requested by Regulatory Authorities) was the Assessment of SpondyloArthritis international Society 40% response (ASAS40) at Week 12. For these geographies, the Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) at Week 52 was moved to the list of secondary efficacy variables. In addition, the following 3 efficacy variables were added to the bottom of the testing hierarchy lists for all countries: -Change from Baseline in ASQoL at Week 52 (elevated from "other" to "secondary" efficacy variable) -Change from Baseline in nocturnal spinal pain Numerical Rating Scale (NRS) at Week 52 (elevated from "other" to "secondary" efficacy variable) -Number of subjects with anterior uveitis (AU) or new AU flares through Week 52 (new variable).
17 December 2018	The purpose of this substantial amendment is to gain additional information about the longerterm disease progress and the effects of CZP treatment in patients with nr-axSpA. To support this, several PROs, a lab assessment, and an additional SI joint MRI will be taken at Week 156/SFE-WD. The visit windows for the SFE Period were also clarified. Additional changes include: -An update to other efficacy variables to include the Week 156/Safety Follow-Up Extension - Withdrawal (SFE-WD) timepoint. SFEWD added to Week 156 instances when needed to distinguish from Week 52/WD. -An update to remove collection of samples for CZP plasma concentration, anti-CZP antibodies, and Biomarkers as this is not done for subjects on alternative treatments. -An update to the subheadings in Section 4.2.2, Section 4.2.3, and Section 4.3 to clarify categorization of variables. -An update to Section 4.4 subheadings to clarify safety variables. -An update of ASDAS-MD to ASDAS-LD (Machado et al, 2018). -Minor editorial and administrative changes have been made throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported