



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:

$0.121 \times$ Back pain (BASDAI Q2 result)

$0.058 \times$ Duration of morning stiffness (BASDAI Q6 result)

$0.110 \times$ Patient's Global Assessment of Disease Activity (PGADA)

$0.073 \times$ Peripheral pain/swelling (BASDAI Q3 result)

$0.579 \times$ (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 DMARD to another; the addition of a 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, 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 | -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 (\pm 0.5) | -4.0 (\pm 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 Extension 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 Extension 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 Extension 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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to the End of Safety Follow-up Extension 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 | 0 / 20 (0.00%) | 10 / 243 (4.12%) | |
| occurrences (all) | 0 | 11 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 15 December 2015 | <p>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.</p> <p>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.</p> |
| 14 March 2016 | <p>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:</p> <ul style="list-style-type: none">-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 | <p>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:</p> <ul style="list-style-type: none"> -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 $\geq 3\times$ upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting $\geq 2\times$ULN total bilirubin in the absence of $\geq 2\times$ULN 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 | <p>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:</p> <ul style="list-style-type: none"> -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 | <p>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.</p> <p>Additional changes include:</p> <ul style="list-style-type: none"> -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