



Clinical trial results:

Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of Certolizumab Pegol in Subjects With Active Axial Spondyloarthritis

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2009-011719-19 |
| Trial protocol | FR DE GB HU BE IT NL CZ |
| Global end of trial date | 18 August 2015 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 |
| This version publication date | 02 September 2016 |
| First version publication date | 02 September 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | AS001 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01087762 |
| 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 | 20 April 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 August 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the efficacy of CZP administered subcutaneously (sc) at the doses of CZP 200mg Q2W every 2 weeks and CZP 400mg Q4W every 4 weeks after a loading dose of CZP 400mg at Weeks 0, 2, and 4 on the signs and symptoms of active axial spondyloarthritis (axSpA).

Protection of trial subjects:

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

Background therapy:

Background therapy was permitted as defined in the study protocol.

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 09 April 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Germany: 29 |
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Poland: 92 |
| Country: Number of subjects enrolled | Czech Republic: 39 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | Argentina: 18 |
| Country: Number of subjects enrolled | Brazil: 6 |
| Country: Number of subjects enrolled | Mexico: 9 |
| Country: Number of subjects enrolled | Canada: 17 |
| Country: Number of subjects enrolled | United States: 71 |
| Worldwide total number of subjects | 325 |
| EEA total number of subjects | 204 |

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) | 317 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This is a multicenter study with 128 sites in North America, Latin America, Western Europe, and Central/Eastern Europe.

325 subjects are included in Randomized Set (RS) shown in Participant Flow for the interim period, and 315 for the final analysis (10 subjects dropped out before receiving a CZP dose), which is an Intention-to-Treat (ITT) dataset.

Pre-assignment

Screening details:

Patients with positive Tuberculosis (TB) tests within Screening Period, but no signs and symptoms of active TB had to be treated with prophylactic TB treatment for at least 4 weeks prior to first study drug administration.

Period 1

| | |
|------------------------------|----------------------------------|
| Period 1 title | Double Blind Period (Weeks 0-24) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Blinding implementation details:

Double Blind (Weeks 0-24), Dose Blind (Weeks 24-48), Open-Label (Weeks 48-204).

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | No |
| Arm title | Placebo |

Arm description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group on Week 16.

After 24 weeks, all subjects were randomized to active treatment with CZP 200 mg every two weeks (Q2W) or CZP 400 mg every four weeks (Q4W).

Placebo : Matching Placebo to CZP injection.

| | |
|--|------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PL |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo administered sc.

| | |
|------------------|----------------|
| Arm title | CZP 200 mg Q2W |
|------------------|----------------|

Arm description:

Subjects received 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.

At every visit, subjects received one injection of 200 mg CZP and one injection of Placebo to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------------|
| Investigational medicinal product name | Certolizumab pegol |
| Investigational medicinal product code | CZP |
| Other name | Cimzia |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: CZP administered sc at a dose of 200mg or 400mg. | |
| Arm title | CZP 400 mg Q4W |

Arm description:

Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 400 mg CZP sc every 4 weeks (Q4W) from Week 8 onwards.

Subjects received 2 injections of Placebo every 4 weeks in between the 2 injections of 200 mg CZP to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Certolizumab pegol |
| Investigational medicinal product code | CZP |
| Other name | Cimzia |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

CZP administered sc at a dose of 200mg or 400mg.

| Number of subjects in period 1 | Placebo | CZP 200 mg Q2W | CZP 400 mg Q4W |
|---------------------------------------|---------|----------------|----------------|
| Started | 107 | 111 | 107 |
| Completed | 95 | 105 | 98 |
| Not completed | 12 | 6 | 9 |
| Consent withdrawn by subject | 1 | 2 | 1 |
| Lost to follow-up | 1 | 2 | 1 |
| SAE, non-fatal | 2 | 2 | 3 |
| Lack of efficacy | 2 | - | 3 |
| Protocol deviation | 6 | - | 1 |

Period 2

| | |
|------------------------------|----------------------------------|
| Period 2 title | Open-Label Period (Weeks 48-204) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Double Blind (Weeks 0-24), Dose Blind (Weeks 24-48), Open-Label (Weeks 48-204).

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | All CZP 200 mg |

Arm description:

All subjects who received CZP at the specified dose (200 mg) at some point during the study, including subjects who were originally randomized to receive placebo and were switched to CZP at Week 16 or Week 24.

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PL |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo administered sc.

| | |
|--|--------------------|
| Investigational medicinal product name | Certolizumab pegol |
| Investigational medicinal product code | CZP |
| Other name | Cimzia |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

CZP administered sc at a dose of 200mg or 400mg.

| | |
|------------------|----------------|
| Arm title | All CZP 400 mg |
|------------------|----------------|

Arm description:

All subjects who received CZP at the specified dose (400 mg) at some point during the study, including subjects who were originally randomized to receive placebo and were switched to CZP at Week 16 or Week 24.

Placebo : Matching Placebo to CZP injection.

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PL |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo administered sc.

| | |
|--|--------------------|
| Investigational medicinal product name | Certolizumab pegol |
| Investigational medicinal product code | CZP |
| Other name | Cimzia |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

CZP administered sc at a dose of 200mg or 400mg.

| Number of subjects in period 2 | All CZP 200 mg | All CZP 400 mg |
|--|----------------|----------------|
| Started | 158 | 157 |
| Completed | 99 | 100 |
| Not completed | 59 | 57 |
| Consent withdrawn by subject | 22 | 15 |
| AE, non-serious non-fatal | 16 | 13 |
| SAE, non-fatal + AE, non-serious/fatal | 2 | 4 |
| Unspecified | 2 | 4 |
| Lost to follow-up | 5 | 2 |
| SAE, non-fatal | 7 | 4 |
| Lack of efficacy | 4 | 14 |
| Protocol deviation | 1 | 1 |

Baseline characteristics

Reporting groups^[1]

| | |
|--|---------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group on Week 16. | |

After 24 weeks, all subjects were randomized to active treatment with CZP 200 mg every two weeks (Q2W) or CZP 400 mg every four weeks (Q4W).

Placebo : Matching Placebo to CZP injection.

| | |
|--|----------------|
| Reporting group title | CZP 200 mg Q2W |
| Reporting group description: | |
| Subjects received 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. At every visit, subjects received one injection of 200 mg CZP and one injection of Placebo to maintain the study blind. | |

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

| | |
|---|----------------|
| Reporting group title | CZP 400 mg Q4W |
| Reporting group description: | |
| Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 400 mg CZP sc every 4 weeks (Q4W) from Week 8 onwards. Subjects received 2 injections of Placebo every 4 weeks in between the 2 injections of 200 mg CZP to maintain the study blind. | |

Placebo : Matching Placebo to CZP injection.

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: Only patients who received at least one dose of CZP were included in the final analysis.

| Reporting group values | Placebo | CZP 200 mg Q2W | CZP 400 mg Q4W |
|-------------------------|---------|----------------|----------------|
| Number of subjects | 107 | 111 | 107 |
| Age Categorical | | | |
| Units: Subjects | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 102 | 110 | 105 |
| >=65 years | 5 | 1 | 2 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.9 | 39.1 | 39.8 |
| standard deviation | ± 12.4 | ± 11.9 | ± 39.9 |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 42 | 44 | 39 |
| Male | 65 | 67 | 68 |

| | | | |
|---|--------------------|---------------------|--------------------|
| Weight Units: kilogram (kg) arithmetic mean standard deviation | 82.142 ± 18.147 | 79.305 ± 18.599 | 83.893 ± 18.855 |
| Height Units: centimeter (cm) arithmetic mean standard deviation | 170.704 ± 9.692 | 171.769 ± 10.171 | 172.753 ± 9.607 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 325 | | |
| Age Categorical Units: Subjects | | | |
| <=18 years | 0 | | |
| Between 18 and 65 years | 317 | | |
| >=65 years | 8 | | |
| Age Continuous Units: years arithmetic mean standard deviation | - | | |
| Gender Categorical Units: Subjects | | | |
| Female | 125 | | |
| Male | 200 | | |
| Weight Units: kilogram (kg) arithmetic mean standard deviation | - | | |
| Height Units: centimeter (cm) arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group on Week 16.

After 24 weeks, all subjects were randomized to active treatment with CZP 200 mg every two weeks (Q2W) or CZP 400 mg every four weeks (Q4W).

Placebo : Matching Placebo to CZP injection.

| | |
|-----------------------|----------------|
| Reporting group title | CZP 200 mg Q2W |
|-----------------------|----------------|

Reporting group description:

Subjects received 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.
At every visit, subjects received one injection of 200 mg CZP and one injection of Placebo to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

| | |
|-----------------------|----------------|
| Reporting group title | CZP 400 mg Q4W |
|-----------------------|----------------|

Reporting group description:

Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 400 mg CZP sc every 4 weeks (Q4W) from Week 8 onwards.
Subjects received 2 injections of Placebo every 4 weeks in between the 2 injections of 200 mg CZP to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

| | |
|-----------------------|----------------|
| Reporting group title | All CZP 200 mg |
|-----------------------|----------------|

Reporting group description:

All subjects who received CZP at the specified dose (200 mg) at some point during the study, including subjects who were originally randomized to receive placebo and were switched to CZP at Week 16 or Week 24.

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

| | |
|-----------------------|----------------|
| Reporting group title | All CZP 400 mg |
|-----------------------|----------------|

Reporting group description:

All subjects who received CZP at the specified dose (400 mg) at some point during the study, including subjects who were originally randomized to receive placebo and were switched to CZP at Week 16 or Week 24.

Placebo : Matching Placebo to CZP injection.

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

| | |
|----------------------------|---------------|
| Subject analysis set title | Placebo (FAS) |
|----------------------------|---------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group on Week 16.

After 24 weeks, all subjects were randomized to active treatment with CZP 200 mg every two weeks (Q2W) or CZP 400 mg every four weeks (Q4W).

Placebo : Matching Placebo to CZP injection.

| | |
|----------------------------|----------------------|
| Subject analysis set title | CZP 200 mg Q2W (FAS) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Subjects received 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.

At every visit, subjects received one injection of 200 mg CZP and one injection of Placebo to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

| | |
|----------------------------|----------------------|
| Subject analysis set title | CZP 400 mg Q4W (FAS) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 400 mg CZP sc every 4 weeks (Q4W) from Week 8 onwards.

Subjects received 2 injections of Placebo every 4 weeks in between the 2 injections of 200 mg CZP to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

| | |
|----------------------------|---|
| Subject analysis set title | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

This arm shows a combination of arm CZP 200 mg Q2W and arm CZP 400 mg Q4W. Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W)/ 400 mg CZP sc every 4 weeks (Q4W) from Week 6/ Week 8 onwards.

Subjects in both CZP arms received additional placebo injections to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | All CZP 200 mg (Safety Analysis) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received CZP at the specified dose (200 mg) at some point during the study, including subjects who were originally randomized to receive placebo and were switched to CZP at Week 16 or Week 24.

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | All CZP 400 mg (Safety Analysis) |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received CZP at the specified dose (400 mg) at some point during the study, including subjects who were originally randomized to receive placebo and were switched to CZP at Week 16 or Week 24.

Placebo : Matching Placebo to CZP injection.

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks

(Q4W).

| | |
|----------------------------|-------------------------|
| Subject analysis set title | All CZP 200 mg + 400 mg |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

This arm shows all patients treated with Certolizumab Pegol (CZP) at least once. Hence, this arm is a combination of arm All CZP 200 mg and arm All CZP 400 mg.

Primary: Assessment in Axial Spondyloarthritis International Society 20 % (ASAS20) response criteria at Week 12

| | |
|-----------------|--|
| End point title | Assessment in Axial Spondyloarthritis International Society 20 % (ASAS20) response criteria at Week 12 |
|-----------------|--|

End point description:

The ASAS20 is defined as an improvement of at least 20 % and absolute improvement of at least 1 unit on a 0 to 10 Numeric Rating Scale (NRS) in at least 3 of the 4 following domains:

- Patient's Global Assessment of Disease Activity
- Pain assessment (total spinal pain)
- Function (represented by Bath Ankylosing Spondylitis Functional Index (BASFI))
- Inflammation (the mean of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questions 5 and 6 concerning morning stiffness intensity and duration)

and absence of deterioration in the potential remaining domain (deterioration is defined as a relative worsening of at least 20 % and an absolute worsening of at least 1 unit).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 12

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|-----------------------------------|----------------------|----------------------|----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 107 | 111 | 107 | 218 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of subjects | 38.3 (29.1 to 47.5) | 57.7 (48.5 to 66.8) | 63.6 (54.4 to 72.7) | 60.6 (54.1 to 67) |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Difference in efficacy |
|----------------------------|------------------------|

Statistical analysis description:

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected.

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

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 ^[1] |
| Method | Wald-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 19.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.3 |
| upper limit | 32.4 |

Notes:

[1] - Difference of Certolizumab Pegol 200 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using a standard two-sided Wald asymptotic test with a 5 % alpha level.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Difference in efficacy |
|-----------------------------------|------------------------|

Statistical analysis description:

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo (FAS) v CZP 400 mg Q4W (FAS) |
| Number of subjects included in analysis | 214 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[2] |
| Method | Wald-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 25.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.3 |
| upper limit | 38.2 |

Notes:

[2] - Difference of Certolizumab Pegol 400 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using a standard two-sided Wald asymptotic test with a 5 % alpha level.

Secondary: Assessment in Axial Spondyloarthritis International Society 20 % (ASAS20) response criteria at Week 24

| | |
|-----------------|--|
| End point title | Assessment in Axial Spondyloarthritis International Society 20 % (ASAS20) response criteria at Week 24 |
|-----------------|--|

End point description:

The ASAS20 is defined as an improvement of at least 20 % and absolute improvement of at least 1 unit on a 0 to 10 Numeric Rating Scale (NRS) in at least 3 of the 4 following domains:

- Patient's Global Assessment of Disease Activity
- Pain assessment (total spinal pain)
- Function (represented by Bath Ankylosing Spondylitis Functional Index (BASFI))
- Inflammation (the mean of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questions 5 and 6 concerning morning stiffness intensity and duration)

and absence of deterioration in the potential remaining domain (deterioration is defined as a relative worsening of at least 20 % and an absolute worsening of at least 1 unit).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 24

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|-----------------------------------|----------------------|----------------------|----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 107 | 111 | 107 | 218 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Percentage of subjects | 29 (20.4 to 37.6) | 66.7 (57.9 to 75.4) | 70.1 (61.4 to 78.8) | 68.3 (62.2 to 74.5) |

Statistical analyses

| Statistical analysis title | Difference in efficacy |
|--|--------------------------------------|
| Statistical analysis description: A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected. | |
| Comparison groups | Placebo (FAS) v CZP 200 mg Q2W (FAS) |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [3] |
| Method | Wald-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 37.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 25.4 |
| upper limit | 50 |

Notes:

[3] - Difference of Certolizumab Pegol 200 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using a standard two-sided Wald asymptotic test with a 5 % alpha level.

| Statistical analysis title | Difference in efficacy |
|--|--------------------------------------|
| Statistical analysis description: A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected. | |
| Comparison groups | Placebo (FAS) v CZP 400 mg Q4W (FAS) |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 214 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[4] |
| Method | Wald-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 41.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 28.9 |
| upper limit | 53.3 |

Notes:

[4] - Difference of Certolizumab Pegol 400 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using a standard two-sided Wald asymptotic test with a 5 % alpha level.

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

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

End point description:

The BASFI assesses physical function in comprising 10 items relating to activities during the past week. Each item ranges from 0 ("Easy") to 10 ("Impossible"). The BASFI is the mean of the 10 scores such that the total score ranges from 0 to 10, with lower scores indicating better physical function. A negative value in BASFI change from Baseline indicates an improvement from Baseline. The higher the negative value the better the improvement.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Week 12

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|--|-----------------------|------------------------|-----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 107 | 111 | 107 | 218 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least square mean | -0.53 (-0.96 to -0.1) | -2.01 (-2.48 to -1.55) | -2.02 (-2.5 to -1.55) | -2.02 (-2.4 to -1.63) |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Difference in efficacy |
|----------------------------|------------------------|

Statistical analysis description:

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected.

| | |
|---|---|
| Comparison groups | Placebo (FAS) v CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[5] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.96 |
| upper limit | -1.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

Notes:

[5] - Difference of CZP 200 mg + 400 mg vs. Placebo was estimated using an ANCOVA model with treatment, region, modified New York criteria and prior TNF-antagonist exposure as factors and Baseline BASFI score as a covariate.

Secondary: Change from Baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 24

| | |
|-----------------|---|
| End point title | Change from Baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 24 |
|-----------------|---|

End point description:

The BASFI assesses physical function in comprising 10 items relating to activities during the past week. Each item ranges from 0 ("Easy") to 10 ("Impossible"). The BASFI is the mean of the 10 scores such that the total score ranges from 0 to 10, with lower scores indicating better physical function. A negative value in BASFI change from Baseline indicates an improvement from Baseline. The higher the negative value the better the improvement.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Week 24

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|--|----------------------|------------------------|----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 107 | 111 | 107 | 218 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least square mean | -0.4 (-0.85 to 0.06) | -2.36 (-2.85 to -1.87) | -2.2 (-2.7 to -1.7) | -2.28 (-2.68 to -1.87) |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Difference in efficacy |
|----------------------------|------------------------|

Statistical analysis description:

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected.

| | |
|---|---|
| Comparison groups | Placebo (FAS) v CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[6] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.38 |
| upper limit | -1.38 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.25 |

Notes:

[6] - Difference of CZP 200 mg + 400 mg vs. Placebo was estimated using an ANCOVA model with treatment, region, modified New York criteria and prior TNF-antagonist exposure as factors and Baseline BASFI score as a covariate.

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

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

End point description:

The BASDAI is a validated self-reported instrument which consists of six 10 unit horizontal Numerical Rating Scales (NRSs) to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration, respectively) over the last week. The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity. A negative value in BASDAI change from Baseline indicates an improvement from Baseline. The higher the negative value the better the improvement.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Week 12

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|--|------------------------|------------------------|-----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 107 | 111 | 107 | 218 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least square mean | -1.22 (-1.65 to -0.78) | -2.82 (-3.29 to -2.35) | -2.8 (-3.28 to -2.33) | -2.81 (-3.2 to -2.43) |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Difference in efficacy |
| Statistical analysis description: A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected. | |
| Comparison groups | Placebo (FAS) v CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[7] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.07 |
| upper limit | -1.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

Notes:

[7] - Difference of CZP 200 mg + 400 mg vs. Placebo was estimated using an ANCOVA model with treatment, region, modified New York criteria and prior TNF-antagonist exposure as factors and Baseline BASDAI score as a covariate.

Secondary: Change from Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 24

| | |
|---|--|
| End point title | Change from Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 24 |
| End point description: The BASDAI is a validated self-reported instrument which consists of six 10 unit horizontal Numerical Rating Scales (NRSs) to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration, respectively) over the last week. The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity. A negative value in BASDAI change from Baseline indicates an improvement from Baseline. The higher the negative value the better the improvement. | |
| End point type | Secondary |
| End point timeframe: From Baseline to Week 24 | |

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|--|----------------------|-----------------------|-----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 107 | 111 | 107 | 218 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least square mean | -1.05 (-1.5 to -0.6) | -3.08 (-3.57 to -2.6) | -3.01 (-3.5 to -2.52) | -3.05 (-3.45 to -2.65) |

Statistical analyses

| Statistical analysis title | Difference in efficacy |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected.

| | |
|---|---|
| Comparison groups | Placebo (FAS) v CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[8] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.49 |
| upper limit | -1.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.25 |

Notes:

[8] - Difference of CZP 200 mg + 400 mg vs. Placebo was estimated using an ANCOVA model with treatment, region, modified New York criteria and prior TNF-antagonist exposure as factors and Baseline BASDAI score as a covariate.

Secondary: Change from Baseline in the Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 12

| | |
|-----------------|--|
| End point title | Change from Baseline in the Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 12 |
|-----------------|--|

End point description:

The BASMI characterizes the spinal mobility of subjects with axial Spondyloarthritis (SpA) and Ankylosing Spondylitis (AS). It is a disease-specific measure consisting of 5 clinical measures to reflect subject axial status: cervical rotation; tragus to wall distance; lateral lumbar flexion; lumbar flexion (modified Schober test); intermalleolar distance. According to the linear definition of the BASMI a score of 0 to 10 is calculated for each item based on the measurement. The mean of the sum of the 5 scores provides the BASMI score. The higher the BASMI score the more severe the patient's limitation of movement due to their axial SpA. A negative value in BASMI change from Baseline indicates an improvement from Baseline. The higher the negative value the better the improvement.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
From Baseline to Week 12

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|--|-----------------------|----------------------|------------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 107 | 111 | 107 | 218 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least square mean | -0.13 (-0.31 to 0.05) | -0.6 (-0.79 to -0.4) | -0.46 (-0.66 to -0.26) | -0.53 (-0.69 to -0.37) |

Statistical analyses

| Statistical analysis title | Difference in efficacy |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected.

| | |
|---|---|
| Comparison groups | Placebo (FAS) v CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[9] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | -0.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1 |

Notes:

[9] - Difference of CZP 200 mg + 400 mg vs. Placebo was estimated using an ANCOVA model with treatment, region, modified New York criteria and prior TNF-antagonist exposure as factors and Baseline BASMI score as a covariate.

Secondary: Change from Baseline in the Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 24

| | |
|-----------------|--|
| End point title | Change from Baseline in the Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 24 |
|-----------------|--|

End point description:

The BASMI characterizes the spinal mobility of subjects with axial SpA and AS. It is a disease-specific measure consisting of 5 clinical measures to reflect subject axial status: cervical rotation; tragus to wall distance; lateral lumbar flexion; lumbar flexion (modified Schober test); intermalleolar distance.

According to the linear definition of the BASMI a score of 0 to 10 is calculated for each item based on the measurement. The mean of the sum of the 5 scores provides the BASMI score. The higher the BASMI score the more severe the patient's limitation of movement due to their axial SpA. A negative value in BASMI change from Baseline indicates an improvement from Baseline. The higher the negative value the better the improvement.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Week 24 | |

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|--|-----------------------|------------------------|----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 107 | 111 | 107 | 218 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Least square mean | -0.07 (-0.27 to 0.12) | -0.54 (-0.75 to -0.34) | -0.49 (-0.7 to 0.28) | -0.52 (-0.69 to -0.34) |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Difference in efficacy |
|-----------------------------------|------------------------|

Statistical analysis description:

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected.

| | |
|---|---|
| Comparison groups | Placebo (FAS) v CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
| Number of subjects included in analysis | 325 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[10] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.66 |
| upper limit | -0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.11 |

Notes:

[10] - Difference of CZP 200 mg + 400 mg vs. Placebo was estimated using an ANCOVA model with treatment, region, modified New York criteria and prior TNF-antagonist exposure as factors and Baseline BASMI score as a covariate.

Secondary: Change from Baseline in the spine Ankylosing Spondylitis spine Magnetic Resonance Imaging (MRI) scoring system for disease

activity (ASspiMRI-a) in the Berlin modification at Week 12

| | |
|-----------------|--|
| End point title | Change from Baseline in the spine Ankylosing Spondylitis spine Magnetic Resonance Imaging (MRI) scoring system for disease activity (ASspiMRI-a) in the Berlin modification at Week 12 |
|-----------------|--|

End point description:

The Berlin modification of the ASspiMRI-a is a scoring system with a concentration on Short-Tau-Inversion Recovery (STIR) sequences without other fat saturation techniques. It quantifies changes in 23 Vertebral Units (VU) of the spine. A VU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of bone marrow edema from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69 with higher scores indicating higher disease activity. A negative value in total spine ASspiMRI-a score change from Baseline indicates an improvement from Baseline. The higher the negative value the higher the reduction of inflammation.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Week 12 | |

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|--------------------------------------|----------------------|----------------------|----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 49 | 47 | 52 | 99 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean | 0.39 (± 4.04) | -3.39 (± 5.59) | -2.16 (± 3.61) | -2.74 (± 4.67) |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The 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. A negative value in SPARCC change from Baseline indicates an improvement from Baseline. The higher the negative value the higher the reduction of inflammation.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Week 12 | |

| End point values | Placebo (FAS) | CZP 200 mg Q2W (FAS) | CZP 400 mg Q4W (FAS) | CZP 200 mg Q2W and CZP 400 mg Q4W (FAS) |
|--------------------------------------|----------------------|----------------------|----------------------|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 45 | 45 | 50 | 95 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean | -1.33 (± 8.33) | -3.61 (± 6.94) | -4.98 (± 8.47) | -4.33 (± 7.77) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from Baseline (Week 0) until study end (Week 204). AEs refer to the Safety Set including all randomized subjects who took at least 1 dose of CZP.

Adverse event reporting additional description:

As per study design, placebo arm subjects shifted either at Week 16 or 24 to CZP treatment. The exposure imbalance across treatment arms could lead to misinterpretation and questionable conclusions comparing simple counts and percentages of AEs. Thus, AEs that were reported while a patient was treated with Placebo are not included.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 14.1 |

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | All CZP 200 mg (Safety Analysis) |
|-----------------------|----------------------------------|

Reporting group description:

All subjects who received CZP at the specified dose (200 mg) at some point during the study, including subjects who were originally randomized to receive placebo and were switched to CZP at Week 16 or Week 24.

Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).

| | |
|-----------------------|----------------------------------|
| Reporting group title | All CZP 400 mg (Safety Analysis) |
|-----------------------|----------------------------------|

Reporting group description:

All subjects who received CZP at the specified dose (400 mg) at some point during the study, including subjects who were originally randomized to receive placebo and were switched to CZP at Week 16 or Week 24.

Placebo : Matching Placebo to CZP injection.

CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

| | |
|-----------------------|-------------------------|
| Reporting group title | All CZP 200 mg + 400 mg |
|-----------------------|-------------------------|

Reporting group description:

This arm shows all patients treated with Certolizumab Pegol (CZP) at least once. Hence, this arm is a combination of arm All CZP 200 mg and arm All CZP 400 mg.

| Serious adverse events | All CZP 200 mg (Safety Analysis) | All CZP 400 mg (Safety Analysis) | All CZP 200 mg + 400 mg |
|---|-------------------------------------|-------------------------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 35 / 158 (22.15%) | 34 / 157 (21.66%) | 69 / 315 (21.90%) |
| 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) | | | |
| Cholesterol granuloma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of the | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Astrocytoma | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Morton's neuroma | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Bone graft | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion induced | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy on contraceptive | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 157 (0.64%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 157 (0.00%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diffuse alveolar damage | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Major depression | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 157 (0.64%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conversion disorder | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus lesion | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Coronary artery disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 157 (0.00%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Hilar lymphadenopathy | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paratracheal lymphadenopathy | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal vein occlusion | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 3 / 157 (1.91%) | 3 / 315 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sigmoiditis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 2 / 157 (1.27%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 2 / 157 (1.27%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis migration | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dermal cyst | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 157 (0.64%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 3 / 158 (1.90%) | 0 / 157 (0.00%) | 3 / 315 (0.95%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankylosing spondylitis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Spondylitis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mycobacterial infection | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 157 (0.64%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemophilus infection | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster disseminated | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia legionella | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 158 (1.90%) | 0 / 157 (0.00%) | 3 / 315 (0.95%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected dermal cyst | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Latent tuberculosis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 157 (0.64%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 157 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | All CZP 200 mg (Safety Analysis) | All CZP 400 mg (Safety Analysis) | All CZP 200 mg + 400 mg |
|---|-------------------------------------|-------------------------------------|----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 142 / 158 (89.87%) | 127 / 157 (80.89%) | 269 / 315 (85.40%) |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 14 / 158 (8.86%) | 17 / 157 (10.83%) | 31 / 315 (9.84%) |
| occurrences (all) | 16 | 23 | 39 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 11 / 158 (6.96%) | 8 / 157 (5.10%) | 19 / 315 (6.03%) |
| occurrences (all) | 14 | 10 | 24 |
| Tuberculin test positive | | | |
| subjects affected / exposed | 8 / 158 (5.06%) | 7 / 157 (4.46%) | 15 / 315 (4.76%) |
| occurrences (all) | 8 | 7 | 15 |
| Aspartate aminotransferase increased | | | |

| | | | |
|--|--|---|--|
| subjects affected / exposed occurrences (all) | 6 / 158 (3.80%) 6 | 8 / 157 (5.10%) 9 | 14 / 315 (4.44%) 15 |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 10 / 158 (6.33%) 18 | 9 / 157 (5.73%) 11 | 19 / 315 (6.03%) 29 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 20 / 158 (12.66%) 26 | 11 / 157 (7.01%) 11 | 31 / 315 (9.84%) 37 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 17 / 158 (10.76%) 25 | 18 / 157 (11.46%) 31 | 35 / 315 (11.11%) 56 |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 7 / 158 (4.43%) 8 | 8 / 157 (5.10%) 11 | 15 / 315 (4.76%) 19 |
| Eye disorders Uveitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) | 11 / 158 (6.96%) 15 5 / 158 (3.16%) 6 | 8 / 157 (5.10%) 12 8 / 157 (5.10%) 9 | 19 / 315 (6.03%) 27 13 / 315 (4.13%) 15 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) | 10 / 158 (6.33%) 13 8 / 158 (5.06%) 8 | 20 / 157 (12.74%) 26 5 / 157 (3.18%) 5 | 30 / 315 (9.52%) 39 13 / 315 (4.13%) 13 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain | 13 / 158 (8.23%) 16 | 11 / 157 (7.01%) 13 | 24 / 315 (7.62%) 29 |

| | | | |
|--|------------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 12 / 158 (7.59%) 15 | 6 / 157 (3.82%) 6 | 18 / 315 (5.71%) 21 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 11 / 158 (6.96%) | 14 / 157 (8.92%) | 25 / 315 (7.94%) |
| occurrences (all) | 15 | 18 | 33 |
| Psoriasis | | | |
| subjects affected / exposed | 8 / 158 (5.06%) | 6 / 157 (3.82%) | 14 / 315 (4.44%) |
| occurrences (all) | 14 | 9 | 23 |
| Eczema | | | |
| subjects affected / exposed | 4 / 158 (2.53%) | 8 / 157 (5.10%) | 12 / 315 (3.81%) |
| occurrences (all) | 6 | 13 | 19 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 9 / 158 (5.70%) | 4 / 157 (2.55%) | 13 / 315 (4.13%) |
| occurrences (all) | 10 | 5 | 15 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 22 / 158 (13.92%) | 11 / 157 (7.01%) | 33 / 315 (10.48%) |
| occurrences (all) | 42 | 20 | 62 |
| Back pain | | | |
| subjects affected / exposed | 14 / 158 (8.86%) | 11 / 157 (7.01%) | 25 / 315 (7.94%) |
| occurrences (all) | 18 | 19 | 37 |
| Spondylitis | | | |
| subjects affected / exposed | 12 / 158 (7.59%) | 13 / 157 (8.28%) | 25 / 315 (7.94%) |
| occurrences (all) | 22 | 14 | 36 |
| Ankylosing spondylitis | | | |
| subjects affected / exposed | 11 / 158 (6.96%) | 5 / 157 (3.18%) | 16 / 315 (5.08%) |
| occurrences (all) | 17 | 8 | 25 |
| Pain in extremity | | | |
| subjects affected / exposed | 10 / 158 (6.33%) | 3 / 157 (1.91%) | 13 / 315 (4.13%) |
| occurrences (all) | 11 | 4 | 15 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 47 / 158 (29.75%) | 43 / 157 (27.39%) | 90 / 315 (28.57%) |
| occurrences (all) | 80 | 83 | 163 |

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|---|-------------------------|-------------------------|--------------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 35 / 158 (22.15%) 53 | 28 / 157 (17.83%) 58 | 63 / 315 (20.00%) 111 |
| Bronchitis subjects affected / exposed occurrences (all) | 24 / 158 (15.19%) 28 | 17 / 157 (10.83%) 18 | 41 / 315 (13.02%) 46 |
| Pharyngitis subjects affected / exposed occurrences (all) | 24 / 158 (15.19%) 36 | 11 / 157 (7.01%) 17 | 35 / 315 (11.11%) 53 |
| Sinusitis subjects affected / exposed occurrences (all) | 17 / 158 (10.76%) 21 | 8 / 157 (5.10%) 10 | 25 / 315 (7.94%) 31 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 10 / 158 (6.33%) 17 | 11 / 157 (7.01%) 15 | 21 / 315 (6.67%) 32 |
| Rhinitis subjects affected / exposed occurrences (all) | 15 / 158 (9.49%) 22 | 6 / 157 (3.82%) 8 | 21 / 315 (6.67%) 30 |
| Influenza subjects affected / exposed occurrences (all) | 9 / 158 (5.70%) 10 | 11 / 157 (7.01%) 14 | 20 / 315 (6.35%) 24 |
| Tonsillitis subjects affected / exposed occurrences (all) | 8 / 158 (5.06%) 10 | 9 / 157 (5.73%) 11 | 17 / 315 (5.40%) 21 |
| Oral herpes subjects affected / exposed occurrences (all) | 9 / 158 (5.70%) 23 | 6 / 157 (3.82%) 7 | 15 / 315 (4.76%) 30 |
| Cystitis subjects affected / exposed occurrences (all) | 8 / 158 (5.06%) 13 | 6 / 157 (3.82%) 10 | 14 / 315 (4.44%) 21 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 5 / 158 (3.16%) 5 | 9 / 157 (5.73%) 9 | 14 / 315 (4.44%) 14 |
| Viral infection subjects affected / exposed occurrences (all) | 9 / 158 (5.70%) 10 | 4 / 157 (2.55%) 4 | 13 / 315 (4.13%) 14 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
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| 23 November 2009 | <p>The following changes were made throughout the protocol:</p> <ul style="list-style-type: none">- Inclusion criteria were broadened to include subjects meeting the ASAS clinical criteria and not limited only to subjects meeting the new ASAS imaging criteria. Subjects meeting the new imaging criteria represented at least 50% of subjects not meeting the mNY classification criteria.- Clarification was included that x-rays and MRIs documenting sacroiliitis for subjects meeting the new ASAS imaging criteria must be read by a radiologist (MRIs) and records (x-rays and MRIs) must be included in source documentation.- Update was made to permit samples collected for measurement of CZP plasma concentration to be possibly used for exploratory biomarker (Dickkopf-related protein 1 [DKK1] and sclerostin) research.- Update was made to Exclusion Criteria 6 and 7 to more clearly define exclusion of subjects with fibromyalgia.- The secondary objective assessment of subject symptomatic state was added, which included the secondary (Patient Acceptable Symptomatic State [PASS] and Physician Acceptable Symptomatic State) and exploratory (Patient's Global Impression of Change [PGIC]) variables.- Update was made to collect SI joint x-ray at Baseline for all subjects not receiving a Baseline MRI.- The schematic of the injection schedule was corrected to remove placebo injection from Week 48 in the CZP 200mg group.- Information on the possible use of other MRI reading criteria in addition to the Spondyloarthritis Research Consortium of Canada (SPARCC) criteria (such as Berlin or modified Berlin criteria) was included.- Clarification was added that the 44 joint counts include both swollen and tender joint counts.- Clarification was added that recording of axSpA history includes relevant family history and prior and concomitant medication history. |

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| 15 March 2010 | <p>The following changes were made throughout the protocol:</p> <ul style="list-style-type: none"> - The Full Analysis Set (FAS) was replaced by the RS for primary efficacy analyses. - The SAP was adjusted for multiple endpoints including implementation of the following: Addition of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Weeks 12 and 24) and Bath Ankylosing Spondylitis Metrology Index (BASMI) (Weeks 12 and 24) to the key secondary variables. <p>A hierarchical test procedure was applied to protect the overall significance level of the multiplicity of dose groups and endpoints with a predefined order of hypotheses testing for the following endpoints: ASAS20 response at Weeks 12 and 24 (200mg Q2W and 400mg Q4W), Bath Ankylosing Spondylitis Functional Index (BASFI) Weeks 12 and 24 (combined dose groups), BASDAI Weeks 12 and 24 (combined dose groups), and BASMI Weeks 12 and 24 (combined dose groups).</p> <ul style="list-style-type: none"> - A marker for inflammation (C-reactive protein [CRP] >upper limit of normal [ULN]) was added to Inclusion Criterion #6. One retesting of subjects failing Screening due to CRP level was permitted. - Clarification was added that SI joint x-rays were performed at Baseline for all subjects. - Update was added that a SI joint x-ray performed <12 weeks (instead of <4 weeks) prior to the Baseline Visit may be used as the Baseline assessment provided that the film can be submitted and meets the requirements for central reading. - Clarification was added that subjects who were enrolled on the basis of meeting the imaging criteria must have been diagnosed on this basis prior to the Screening Visit. - Clarification was added that abatacept was both a prohibited medication (if used within 3 months prior to Baseline) and a prohibited concomitant and rescue treatment. - For TB testing, inconsistencies in visit referencing (eg, Baseline) with regards to purified protein derivative (PPD) tests were corrected to reference the Screening Visit. <p>(Continued below)</p> |
| 15 March 2010 | <p>(Global Substantial Protocol Amendment #3 - 15-Mar-2010 - belongs to the Global Amendment #2)</p> <ul style="list-style-type: none"> - Clarification that the cited liver function tests (LFTs) >2xULN, creatinine >ULN, or white blood cells (WBCs) <3.0x10⁹/L represent examples of clinically significant laboratory abnormalities which would exclude subject entry into the study was added to Exclusion Criterion #29. - The statement requiring x-ray or MRI documenting sacroiliitis within 6 months of Screening was removed. - Clarification was added that rescreening of subjects with latent TB who were unable to complete a minimum of 4 weeks of TB therapy within the Screening Period was permitted. - Clarification was added that in addition to the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS), x-rays could be evaluated using other assessments. - Clarification was added that subjects meeting the definite AS diagnosis according to the mNY classification criteria were defined as subjects meeting the NY classification criteria in the context of this protocol. - Clarification on the definition for inflammatory back pain for axSpA was added. |

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| 06 December 2010 | <p>The following changes were made throughout the protocol:</p> <ul style="list-style-type: none"> - The approximate number of subjects to be screened was increased from 400 to 600. - The approximate number of sites participating in the study was increased from 100 to 130. - Inclusion Criterion #5 was clarified to ensure that the symptom duration of adult-onset axSpA was at least 3 months and to reduce confusion about the requirements of the study population. - Inclusion Criterion #6 (and the respective study population information) was expanded to include subjects with MRI evidence of sacroiliitis. - Select sites could conduct prescreening activities, and prior to these activities, subjects were to read and sign a separate informed consent form that had been approved by an IEC/IRB and the Sponsor and which complied with regulatory requirements. - The specification for vital signs to be collected within 15 minutes prior to dosing was removed. - In several locations in the protocol, it was clarified that pregnancy testing should be done on women of childbearing potential. - It was clarified that the TB test would be repeated at Week 48 and Week 96 for subjects with a previously negative test result. - As the batch number was not included on the label, this information was removed from the labeling section of the protocol. - It was clarified that Investigators and subjects would remain blind to the assigned CZP dose regimen until the subject reaches the Week 48 Visit. - The sample size for each treatment group required to detect statistically significant differences in ASAS20 was changed from 100 to 105 because of a previous FDA request that the primary analysis population be changed from FAS to all randomized subjects. - Sponsor personnel and the corresponding contact information were updated. - Various administrative adjustments for internal consistency were made. |
| 27 April 2011 | <p>The following global changes were made throughout the protocol:</p> <ul style="list-style-type: none"> - The company name was changed from SCHWARZ BIOSCIENCES, GmbH, A Member of the UCB Group of Companies, to UCB BIOSCIENCES GmbH. - Addition of the requirement for MRI at Week 48. - The addition of a second interim analysis after all subjects complete Week 48. |

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| 18 January 2013 | <p>Protocol Amendment 5 (18 Jan 2013) was implemented to extend the open-label period for an additional 48 weeks. In order to obtain more information about the long-term impact of the use of CZP on structural damage spine x-ray, SI joint x-ray and MRI should have been repeated at the Completion Visit (or Early Withdrawal Visit).</p> <p>Within this amendment, new UCB internal standards for procedures regarding TB detection and monitoring were implemented in order to comply with the revised UCB policy applied to all UCBsponsored studies that included subjects with immunological diseases, who were at increased risk of TB infection either associated with the investigational drug, underlying disease, concomitant treatments, or other medical or sociological factors. These instructions are evidence-based and reflect the updated recommendations of various national guidelines Centers for Disease Control and Prevention diagnosis of latent TB infection.</p> <p>With respect to new scientific evidence, the list of biomarkers that may be of interest for later analysis was updated and alternative methods of analysis of CZP and its constituent moieties were added.</p> <p>The following global changes were made throughout the protocol:</p> <ul style="list-style-type: none"> - New Clinical Project Manager, Biostatistician, and Clinical Program Director. - Wording regarding the extension of the open-label period. - Wording regarding the additional Investigations. - Wording regarding the new TB standards. - List of biomarkers that may be of interest for analysis was updated. - Visit scheduling of Week 158 (Completion/Early Withdrawal Visit) was shifted to Week 204 and last dosing visit at Week 156 now occurred at Week 202 for the Q2W regimen and Week 200 for the Q4W regimen. Regular last on-site visit and the final evaluation visit were combined to reduce the amount of investigations. - Chest x-ray was requested additionally at Week 156 and at Completion Visit (Week 204)/Early Withdrawal. <p>(Continued below)</p> |
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| 18 January 2013 | <p>(Global Substantial Protocol Amendment #7 - 18-Jan-2013 - belongs to the Global Amendment #6)</p> <ul style="list-style-type: none"> - Spine x-ray, SI joint x-ray and MRI of spine and SI-joint were requested at the Completion Visit Week 204/Early Withdrawal. - Injections should have been administered having a minimum of 10 days between CZP 200mg Q2W injections and a minimum of 20 days between CZP 400mg Q4W injections. - Injections missed due to a reasonable interfering adverse event (AE), that did not allow administration of an anti-TNF due to safety reasons, were not to have been considered for the evaluation of subject compliance. - An error in the description of the ASAS definition was corrected in Section 9.1.1 (of the protocol). <p>Interim analyses of database lock 1 and 2 were performed with the hereby corrected parameters according to the international standards. The modified definition as described within Protocol Amendment 4 was evaluated additionally in the interim analysis of database lock 1 only.</p> <ul style="list-style-type: none"> - An error in the description of the BASMI evaluation in Section 9.1.8 (of the protocol) was corrected. <p>Now the description matches the naming of the "linear BASMI" according to secondary efficacy variables described in Section 4.1.2 (of the protocol).</p> <ul style="list-style-type: none"> - The AE of interest Section 11.3 (of the protocol) was updated to be consistent with current reporting requirements. |
| 15 March 2013 | Protocol Amendment 6 implemented administrative changes to correct errors that existed in Protocol Amendment 5. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported