



## Clinical trial results:

**Prediction of response to Certolizumab Pegol treatment by functional MRI of the brain. A multi-center, randomized double-blind controlled study**

**Prediction of response to Certolizumab-Pegol in RA (PreCePRA)**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2013-000337-13  |
| Trial protocol           | DE PT           |
| Global end of trial date | 10 January 2020 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 14 November 2021 |
| First version publication date | 14 November 2021 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | PreCePra |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01864265 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                           |
|------------------------------|-----------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Universitätsklinikum Erlangen                                                                             |
| Sponsor organisation address | Maximiliansplatz 2, Erlangen, Germany, 91054                                                              |
| Public contact               | Clinical Trial Unit, Med. 3 , Universitätsklinikum Erlangen, +49 91318543014, juergen.rech@uk-erlangen.de |
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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                       | 18 July 2021    |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 10 January 2020 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 10 January 2020 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary parameter of interest is the proportion of patients who reach low disease activity according to the DAS28 (DAS28 < 3.2) during the first 12 weeks of study participation according their baseline CNS activity measured by functional MRI.

Protection of trial subjects:

All patients must sign and date the most current IRB/IEC-approved written informed consent form (ICF) Review patient eligibility and ensure that all inclusion and exclusion criteria are met.

Physical examination, including pulse rate, systolic and diastolic blood pressure (after the patient has been in a semi-supine position for at least 5 minutes), body temperature, body weight and physician's global assessment of disease status

ECG: a 12-lead ECG with formal readings. Patients should be supine for 5 minutes before the recording is performed

TB testing will be performed according to local guidelines. In case of a positive TB test, requiring treatment for latent TB, the patient must be treated at a minimum of 4 weeks or even longer (according to national and international guidelines) before starting treatment with the TNF-inhibitor (Certolizumab-Pegol). If treatment of latent TB is required re-screening of the patient is possible. Blood samples for laboratory tests including High Sensitivity C-Reactive Protein, Erythrocyte Sedimentation Rate.

Rheumatoid factor and CCP-antibodies

Cytokines and Hormones of the hypothalamic-pituitary-adrenal/gonadal axis (IL-6, TNF, IFN-gamma, cortisol, ACTH und NPY) and urinalysis (specific gravity, pH, glucose, protein, ketones, bilirubin).

Hematology: Hematology includes complete blood count (RBC count, hemoglobin, hematocrit, WBC count and differential, absolute

Pregnancy, any event with elevated risk of interaction with immunosuppressive therapy such as myocardial infarction, pulmonary embolism, apoplexy; medical emergencies requiring immediate treatment as an inpatient and / or surgery (severe traffic accident, ileus, etc.), and infectious diseases requiring anti-inflammatory therapy risking interaction with immunosuppressive therapy. It is incumbent upon the Investigator to consider continuation or discontinuation of therapy.

Background therapy:

- Glucocorticoids treatment up to 10mg prednisolone per day will be allowed at study entry.
- At screening- visit patients should have been treated without alterations of DMARD therapy (for at least three months) (i.e. Methotrexate) (with or without concomitant use of steroids).

Evidence for comparator:

Study Rationale

By using functional MRI we have recently shown that TNFi elicit rapid changes in brain function linked to the perception of RA. Functional MRI allows the detection of tiny changes in neuronal activity by measuring alterations of blood flow in the context of neuronal activation. TNFi rapidly reversed the widespread activation of brain centers involved in pain such as the thalamus and the somatosensory cortex, as well as those involved in the control, of mood and emotions such as the limbic system. Moreover, as small phase I study with 10 patients with RA showed that high brain activity detected in the functional MRI predicts clinical response to Certolizumab Pegol after 1 month, suggesting the central nervous system activity may be used as a tool to predict response to TNFi . The rationale of this study is to test whether response to TNFi can be predicted by using functional MRI.

Risk-Benefit considerations

The introduction of TNF  $\alpha$  antagonists represents a major advance in the drug treatment of RA. The therapeutic response to currently available TNF  $\alpha$  antagonists is idiosyncratic. This is also true for tolerability and is in keeping with the well known idiosyncratic response to traditional DMARDs. Therefore, there remains a medical need for additional effective TNF  $\alpha$  antagonists for the treatment of RA.

The benefit of the protocol PreCePra are the potential future availability of a predictor before treating

patients and to predict that these patients treated with certolizumab pegol will respond to the TNF  $\alpha$  blockade.

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 01 June 2013 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Portugal: 1  |
| Country: Number of subjects enrolled | Germany: 105 |
| Country: Number of subjects enrolled | Serbia: 50   |
| Worldwide total number of subjects   | 156          |
| EEA total number of subjects         | 106          |

Notes:

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#### Subjects enrolled per age group

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|                                           |     |
|-------------------------------------------|-----|
| 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)                      | 148 |
| From 65 to 84 years                       | 8   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Patient recruitment was performed in the outpatient and inpatient ward of the Medizinische Klinik 3, Universitätsklinikum Erlangen, as well as in the participating centers.

### Pre-assignment

Screening details:

156 patients signed written informed consent. 13 patients did not meet inclusion-exclusion criteria or did not meet inclusion exclusion criteria. 143 subjects reached baseline visit.

### Period 1

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 1 title               | Baseline                                                      |
| Is this the baseline period? | Yes                                                           |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

The password-protected and/or encrypted electronic master randomization list is kept by Clinical Site (pharmacist) in their secure system and is only accessible to the randomization list manager. No open key to the code will be available at the study centre, fMRI analyst, to the CRO monitors or to the project team at UCB-PHARMA, neither to the sponsor.

### Arms

|                              |                                  |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes                              |
| <b>Arm title</b>             | Group 1 (high voxel count + CZP) |

Arm description:

fMRI: high voxel count; randomized to: Certolizumab Pegol

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Certolizumab Pegol (Cimzia®) |
| Investigational medicinal product code | L04AB05                      |
| Other name                             |                              |
| Pharmaceutical forms                   | Solution for injection       |
| Routes of administration               | Subcutaneous use             |

Dosage and administration details:

Loading dose:

The recommended starting dose of Cimzia® for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. MTX should be continued during treatment with Cimzia® where appropriate.

Maintenance dose:

The recommended maintenance dose of Cimzia® for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia® where appropriate.

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Group 2 (low voxel count + CZP) |
|------------------|---------------------------------|

Arm description:

fMRI: low voxel Count; randomized to: Certolizumab Pegol

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Certolizumab Pegol (Cimzia®) |
| Investigational medicinal product code | L04AB05                      |
| Other name                             |                              |
| Pharmaceutical forms                   | Solution for injection       |
| Routes of administration               | Subcutaneous use             |

Dosage and administration details:

Loading dose:

The recommended starting dose of Cimzia® for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. MTX should be continued during treatment with Cimzia® where appropriate.

Maintenance dose:

The recommended maintenance dose of Cimzia® for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia® where appropriate.

|                  |                                             |
|------------------|---------------------------------------------|
| <b>Arm title</b> | Group 3 (high or low voxel count + placebo) |
|------------------|---------------------------------------------|

Arm description:

fMRI: high or low voxel Count; randomized to: placebo

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

Dosage and administration details:

one injection every two weeks until week 12

| Number of subjects in period 1 | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |
|--------------------------------|----------------------------------|---------------------------------|---------------------------------------------|
|                                |                                  |                                 |                                             |
| Started                        | 52                               | 52                              | 52                                          |
| Completed                      | 49                               | 48                              | 46                                          |
| Not completed                  | 3                                | 4                               | 6                                           |
| Physician decision             | -                                | 4                               | 6                                           |
| Protocol deviation             | 3                                | -                               | -                                           |

## Period 2

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 2 title               | Treatment Period 1 (week 0 - 12)                              |
| Is this the baseline period? | No                                                            |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

## Arms

|                              |                                  |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes                              |
| <b>Arm title</b>             | Group 1 (high voxel count + CZP) |

Arm description:

fMRI: high voxel Count; randomized to: Certolizumab Pegol

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Certolizumab Pegol (Cimzia®) |
| Investigational medicinal product code | L04AB05                      |
| Other name                             |                              |
| Pharmaceutical forms                   | Solution for injection       |
| Routes of administration               | Subcutaneous use             |

**Dosage and administration details:****Loading dose:**

The recommended starting dose of Cimzia® for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. MTX should be continued during treatment with Cimzia® where appropriate.

**Maintenance dose:**

The recommended maintenance dose of Cimzia® for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia® where appropriate.

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Group 2 (low voxel count + CZP) |
|------------------|---------------------------------|

**Arm description:**

fMRI: low voxel Count; randomized to: Certolizumab Pegol

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Certolizumab Pegol (Cimzia®) |
| Investigational medicinal product code | L04AB05                      |
| Other name                             |                              |
| Pharmaceutical forms                   | Solution for injection       |
| Routes of administration               | Subcutaneous use             |

**Dosage and administration details:****Loading dose:**

The recommended starting dose of Cimzia® for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. MTX should be continued during treatment with Cimzia® where appropriate.

**Maintenance dose:**

The recommended maintenance dose of Cimzia® for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia® where appropriate.

|                  |                                             |
|------------------|---------------------------------------------|
| <b>Arm title</b> | Group 3 (high or low voxel count + placebo) |
|------------------|---------------------------------------------|

**Arm description:**

fMRI: high or low voxel Count; randomized to: placebo

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             | Saline 0,9%            |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

one Syringe every 2 weeks

| Number of subjects in period 2 | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |
|--------------------------------|----------------------------------|---------------------------------|---------------------------------------------|
|                                |                                  |                                 |                                             |
| Started                        | 49                               | 48                              | 46                                          |
| Completed                      | 48                               | 45                              | 46                                          |
| Not completed                  | 1                                | 3                               | 0                                           |
| Consent withdrawn by subject   | 1                                | -                               | -                                           |
| Adverse event, non-fatal       | -                                | 3                               | -                                           |

**Period 3**

|                              |                                                        |
|------------------------------|--------------------------------------------------------|
| Period 3 title               | Treatment Period 2 (week 12 - 24)                      |
| Is this the baseline period? | No                                                     |
| Allocation method            | Randomised - controlled                                |
| Blinding used                | Double blind                                           |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Assessor |

**Arms**

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Group 1 (high voxel count + CZP) |
|------------------|----------------------------------|

Arm description:

fMRI: high voxel Count; randomized to : Certolizumab Pegol; responder at week 12

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Certolizumab Pegol (Cimzia®) |
| Investigational medicinal product code | L04AB05                      |
| Other name                             |                              |
| Pharmaceutical forms                   | Solution for injection       |
| Routes of administration               | Subcutaneous use             |

Dosage and administration details:

Maintenance dose:

The recommended maintenance dose of Cimzia® for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia® where appropriate.

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Group 2 (low voxel count + CZP) |
|------------------|---------------------------------|

Arm description:

fMRI: low voxel Count; randomized to : Certolizumab Pegol; responder at week 12

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Certolizumab Pegol (Cimzia®) |
| Investigational medicinal product code | L04AB05                      |
| Other name                             |                              |
| Pharmaceutical forms                   | Solution for injection       |
| Routes of administration               | Subcutaneous use             |

Dosage and administration details:

Maintenance dose:

The recommended maintenance dose of Cimzia® for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia® where appropriate.

|                  |                                             |
|------------------|---------------------------------------------|
| <b>Arm title</b> | Group 3 (high or low voxel count + placebo) |
|------------------|---------------------------------------------|

Arm description:

fMRI: high or low voxel Count; randomized to : placebo; non-responder at week 12; Certolizumab Pegol from week 12 to 24

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | placebo -> experimental      |
| Investigational medicinal product name | Certolizumab Pegol (Cimzia®) |
| Investigational medicinal product code | L04AB05                      |
| Other name                             |                              |
| Pharmaceutical forms                   | Solution for injection       |
| Routes of administration               | Subcutaneous use             |

Dosage and administration details:

Loading dose:

The recommended starting dose of Cimzia® for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. MTX should be continued during treatment with Cimzia® where appropriate.

Maintenance dose:

The recommended maintenance dose of Cimzia® for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia® where appropriate.

| Number of subjects in period 3 | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |
|--------------------------------|----------------------------------|---------------------------------|---------------------------------------------|
|                                |                                  |                                 |                                             |
| Started                        | 48                               | 45                              | 46                                          |
| Completed                      | 38                               | 35                              | 39                                          |
| Not completed                  | 10                               | 10                              | 7                                           |
| Lack of efficacy               | 10                               | 10                              | 7                                           |

## Baseline characteristics

### Reporting groups

|                                                                                           |                                             |
|-------------------------------------------------------------------------------------------|---------------------------------------------|
| Reporting group title                                                                     | Group 1 (high voxel count + CZP)            |
| Reporting group description:<br>fMRI: high voxel count; randomized to: Certolizumab Pegol |                                             |
| Reporting group title                                                                     | Group 2 (low voxel count + CZP)             |
| Reporting group description:<br>fMRI: low voxel Count; randomized to: Certolizumab Pegol  |                                             |
| Reporting group title                                                                     | Group 3 (high or low voxel count + placebo) |
| Reporting group description:<br>fMRI: high or low voxel Count; randomized to: placebo     |                                             |

| Reporting group values                                                                                                                                                                                                                                    | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|
| Number of subjects                                                                                                                                                                                                                                        | 52                               | 52                              | 52                                          |
| Age categorical                                                                                                                                                                                                                                           |                                  |                                 |                                             |
| Patients must be aged $\geq 18$ years at time of consent                                                                                                                                                                                                  |                                  |                                 |                                             |
| Units: Subjects                                                                                                                                                                                                                                           |                                  |                                 |                                             |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                  |                                 |                                             |
| Age continuous                                                                                                                                                                                                                                            |                                  |                                 |                                             |
| Units: years                                                                                                                                                                                                                                              |                                  |                                 |                                             |
| arithmetic mean                                                                                                                                                                                                                                           | 54.3                             | 56.5                            | 52.1                                        |
| standard deviation                                                                                                                                                                                                                                        | $\pm 10.8$                       | $\pm 12.2$                      | $\pm 12.0$                                  |
| Gender categorical                                                                                                                                                                                                                                        |                                  |                                 |                                             |
| Units: Subjects                                                                                                                                                                                                                                           |                                  |                                 |                                             |
| Female                                                                                                                                                                                                                                                    | 38                               | 37                              | 33                                          |
| Male                                                                                                                                                                                                                                                      | 14                               | 15                              | 19                                          |
| ACPA                                                                                                                                                                                                                                                      |                                  |                                 |                                             |
| Units: Subjects                                                                                                                                                                                                                                           |                                  |                                 |                                             |
| positive                                                                                                                                                                                                                                                  | 34                               | 40                              | 40                                          |
| negative                                                                                                                                                                                                                                                  | 18                               | 12                              | 12                                          |
| RF                                                                                                                                                                                                                                                        |                                  |                                 |                                             |
| Units: Subjects                                                                                                                                                                                                                                           |                                  |                                 |                                             |
| positive                                                                                                                                                                                                                                                  | 35                               | 38                              | 36                                          |
| negative                                                                                                                                                                                                                                                  | 17                               | 14                              | 16                                          |
| Tender joints (28)                                                                                                                                                                                                                                        |                                  |                                 |                                             |
| Units: joints                                                                                                                                                                                                                                             |                                  |                                 |                                             |
| arithmetic mean                                                                                                                                                                                                                                           | 9.3                              | 11.3                            | 9.9                                         |

|                      |        |        |        |
|----------------------|--------|--------|--------|
| standard deviation   | ± 6.4  | ± 6.7  | ± 6.2  |
| Swollen joints       |        |        |        |
| Units: joints        |        |        |        |
| arithmetic mean      | 7.0    | 8.7    | 8.0    |
| standard deviation   | ± 4.4  | ± 6.3  | ± 4.8  |
| Patient global VAS   |        |        |        |
| Units: mm            |        |        |        |
| arithmetic mean      | 57.2   | 59.1   | 57.6   |
| standard deviation   | ± 19.9 | ± 17.8 | ± 22.5 |
| Physician global VAS |        |        |        |
| Units: mm            |        |        |        |
| arithmetic mean      | 46.0   | 49.5   | 53.1   |
| standard deviation   | ± 20.2 | ± 19.2 | ± 16.2 |
| Pain VAS             |        |        |        |
| Units: mm            |        |        |        |
| arithmetic mean      | 53.5   | 57.1   | 54.9   |
| standard deviation   | ± 18.0 | ± 17.0 | ± 22.7 |
| ESR                  |        |        |        |
| Units: mm/h          |        |        |        |
| arithmetic mean      | 23.7   | 25.2   | 28.2   |
| standard deviation   | ± 19.0 | ± 17.1 | ± 23.2 |
| CRP                  |        |        |        |
| Units: mg/l          |        |        |        |
| arithmetic mean      | 6.8    | 7.9    | 11.2   |
| standard deviation   | ± 12.7 | ± 8.7  | ± 16.5 |
| DAS28                |        |        |        |
| Units: none          |        |        |        |
| arithmetic mean      | 4.7    | 5.0    | 4.9    |
| standard deviation   | ± 1.0  | ± 1.1  | ± 1.0  |

|                                                       |       |  |  |
|-------------------------------------------------------|-------|--|--|
| <b>Reporting group values</b>                         | Total |  |  |
| Number of subjects                                    | 156   |  |  |
| Age categorical                                       |       |  |  |
| Patients must be aged ≥ 18 years at time of consent   |       |  |  |
| Units: Subjects                                       |       |  |  |
| In utero                                              | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                                  | 0     |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0     |  |  |
| Children (2-11 years)                                 | 0     |  |  |
| Adolescents (12-17 years)                             | 0     |  |  |
| Adults (18-64 years)                                  | 0     |  |  |
| From 65-84 years                                      | 0     |  |  |
| 85 years and over                                     | 0     |  |  |
| Age continuous                                        |       |  |  |
| Units: years                                          |       |  |  |
| arithmetic mean                                       |       |  |  |
| standard deviation                                    | -     |  |  |

|                                                                              |     |  |  |
|------------------------------------------------------------------------------|-----|--|--|
| Gender categorical<br>Units: Subjects                                        |     |  |  |
| Female                                                                       | 108 |  |  |
| Male                                                                         | 48  |  |  |
| ACPA<br>Units: Subjects                                                      |     |  |  |
| positive                                                                     | 114 |  |  |
| negative                                                                     | 42  |  |  |
| RF<br>Units: Subjects                                                        |     |  |  |
| positive                                                                     | 109 |  |  |
| negative                                                                     | 47  |  |  |
| Tender joints (28)<br>Units: joints<br>arithmetic mean<br>standard deviation | -   |  |  |
| Swollen joints<br>Units: joints<br>arithmetic mean<br>standard deviation     | -   |  |  |
| Patient global VAS<br>Units: mm<br>arithmetic mean<br>standard deviation     | -   |  |  |
| Physician global VAS<br>Units: mm<br>arithmetic mean<br>standard deviation   | -   |  |  |
| Pain VAS<br>Units: mm<br>arithmetic mean<br>standard deviation               | -   |  |  |
| ESR<br>Units: mm/h<br>arithmetic mean<br>standard deviation                  | -   |  |  |
| CRP<br>Units: mg/l<br>arithmetic mean<br>standard deviation                  | -   |  |  |
| DAS28<br>Units: none<br>arithmetic mean<br>standard deviation                | -   |  |  |

## End points

### End points reporting groups

|                                                                                                                                                         |                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Reporting group title                                                                                                                                   | Group 1 (high voxel count + CZP)            |
| Reporting group description:<br>fMRI: high voxel count; randomized to: Certolizumab Pegol                                                               |                                             |
| Reporting group title                                                                                                                                   | Group 2 (low voxel count + CZP)             |
| Reporting group description:<br>fMRI: low voxel Count; randomized to: Certolizumab Pegol                                                                |                                             |
| Reporting group title                                                                                                                                   | Group 3 (high or low voxel count + placebo) |
| Reporting group description:<br>fMRI: high or low voxel Count; randomized to: placebo                                                                   |                                             |
| Reporting group title                                                                                                                                   | Group 1 (high voxel count + CZP)            |
| Reporting group description:<br>fMRI: high voxel Count; randomized to: Certolizumab Pegol                                                               |                                             |
| Reporting group title                                                                                                                                   | Group 2 (low voxel count + CZP)             |
| Reporting group description:<br>fMRI: low voxel Count; randomized to: Certolizumab Pegol                                                                |                                             |
| Reporting group title                                                                                                                                   | Group 3 (high or low voxel count + placebo) |
| Reporting group description:<br>fMRI: high or low voxel Count; randomized to: placebo                                                                   |                                             |
| Reporting group title                                                                                                                                   | Group 1 (high voxel count + CZP)            |
| Reporting group description:<br>fMRI: high voxel Count; randomized to : Certolizumab Pegol; responder at week 12                                        |                                             |
| Reporting group title                                                                                                                                   | Group 2 (low voxel count + CZP)             |
| Reporting group description:<br>fMRI: low voxel Count; randomized to : Certolizumab Pegol; responder at week 12                                         |                                             |
| Reporting group title                                                                                                                                   | Group 3 (high or low voxel count + placebo) |
| Reporting group description:<br>fMRI: high or low voxel Count; randomized to : placebo; non-responder at week 12; Certolizumab Pegol from week 12 to 24 |                                             |

### Primary: Low disease activity (DAS28 < 3.2) at week 12, proportion

|                                                                                                                                                                                 |                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| End point title                                                                                                                                                                 | Low disease activity (DAS28 < 3.2) at week 12, proportion |
| End point description:<br>Proportion of patients who reach low disease activity (DAS28 < 3.2) during the first 12 weeks according their screening CNS activity measured by fMRI |                                                           |
| End point type                                                                                                                                                                  | Primary                                                   |
| End point timeframe:<br>week 12                                                                                                                                                 |                                                           |

| End point values            | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|-----------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type          | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed | 42                               | 46                              | 46                                          |  |
| Units: subjects             | 17                               | 14                              | 12                                          |  |

## Statistical analyses

| Statistical analysis title                                                              | Comparison DAS28 < 3.2 Group 1 vs. 3                                           |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Statistical analysis description:<br>Comparison DAS28 < 3.2 between group 1 and group 3 |                                                                                |
| Comparison groups                                                                       | Group 1 (high voxel count + CZP) v Group 3 (high or low voxel count + placebo) |
| Number of subjects included in analysis                                                 | 88                                                                             |
| Analysis specification                                                                  | Pre-specified                                                                  |
| Analysis type                                                                           |                                                                                |
| P-value                                                                                 | = 0.6433                                                                       |
| Method                                                                                  | Chi-squared                                                                    |

| Statistical analysis title              | Comparison DAS28 < 3.2 Group 2 vs. 3                                          |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Comparison groups                       | Group 2 (low voxel count + CZP) v Group 3 (high or low voxel count + placebo) |
| Number of subjects included in analysis | 92                                                                            |
| Analysis specification                  | Pre-specified                                                                 |
| Analysis type                           |                                                                               |
| P-value                                 | = 0.1515                                                                      |
| Method                                  | Chi-squared                                                                   |

## Secondary: Low disease activity (DAS28 < 3.2) at week 24, proportion

| End point title                                                                                                                                                                 | Low disease activity (DAS28 < 3.2) at week 24, proportion |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| End point description:<br>Proportion of patients who reach low disease activity (DAS28 < 3.2) during the first 24 weeks according their screening CNS activity measured by fMRI |                                                           |
| End point type                                                                                                                                                                  | Secondary                                                 |
| End point timeframe:<br>week 24                                                                                                                                                 |                                                           |

| End point values            | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|-----------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type          | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed | 34                               | 32                              | 39                                          |  |
| Units: subjects             | 24                               | 17                              | 21                                          |  |

## Statistical analyses

|                                         |                                                                                                                  |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Low disease activity (DAS28 < 3.2)                                                                               |
| Comparison groups                       | Group 1 (high voxel count + CZP) v Group 2 (low voxel count + CZP) v Group 3 (high or low voxel count + placebo) |
| Number of subjects included in analysis | 105                                                                                                              |
| Analysis specification                  | Pre-specified                                                                                                    |
| Analysis type                           | other <sup>[1]</sup>                                                                                             |
| P-value                                 | = 0.25                                                                                                           |
| Method                                  | Chi-squared                                                                                                      |

Notes:

[1] - Chi-squared

## Secondary: Remission (DAS28 < 2.6) at week 12, proportion

|                        |                                                                                                                                            |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Remission (DAS28 < 2.6) at week 12, proportion                                                                                             |
| End point description: | Proportion of patients who reach remission (DAS28 < 2.6) during the first 12 weeks according their screening CNS activity measured by fMRI |
| End point type         | Secondary                                                                                                                                  |
| End point timeframe:   | week 12                                                                                                                                    |

| End point values            | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|-----------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type          | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed | 48                               | 40                              | 46                                          |  |
| Units: subjects             | 12                               | 13                              | 6                                           |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Remission (DAS28 < 2.6) at week 24, proportion

|                        |                                                                                                    |
|------------------------|----------------------------------------------------------------------------------------------------|
| End point title        | Remission (DAS28 < 2.6) at week 24, proportion                                                     |
| End point description: | Proportion of patients who reach remission (DAS28 < 2.6) during the first 24 weeks according their |

screening CNS activity measured by fMRI

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| week 24              |           |

| End point values            | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|-----------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type          | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed | 38                               | 28                              | 39                                          |  |
| Units: subjects             | 19                               | 8                               | 10                                          |  |

## Statistical analyses

|                                         |                                                                                                                  |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title              | Remission at week 24                                                                                             |
| Comparison groups                       | Group 1 (high voxel count + CZP) v Group 2 (low voxel count + CZP) v Group 3 (high or low voxel count + placebo) |
| Number of subjects included in analysis | 105                                                                                                              |
| Analysis specification                  | Post-hoc                                                                                                         |
| Analysis type                           | other <sup>[2]</sup>                                                                                             |
| P-value                                 | < 0.009                                                                                                          |
| Method                                  | Chi-squared                                                                                                      |

Notes:

[2] - Chi squared

## Secondary: DAS28 at week 12, mean

|                        |                        |
|------------------------|------------------------|
| End point title        | DAS28 at week 12, mean |
| End point description: |                        |
| Mean DAS28 at week 12  |                        |
| End point type         | Secondary              |
| End point timeframe:   |                        |
| week 12                |                        |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 3.3 (± 1.2)                      | 3.8 (± 1.4)                     | 4.1 (± 1.5)                                 |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DAS28 at week 24, mean

|                                                 |                        |
|-------------------------------------------------|------------------------|
| End point title                                 | DAS28 at week 24, mean |
| End point description:<br>Mean DAS28 at week 24 |                        |
| End point type                                  | Secondary              |
| End point timeframe:<br>week 24                 |                        |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 2.79 ( $\pm$ 1.11)               | 3.2 ( $\pm$ 1.11)               | 3.11 ( $\pm$ 0.95)                          |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 emotional well-being at week 12, mean

|                                                                      |                                             |
|----------------------------------------------------------------------|---------------------------------------------|
| End point title                                                      | SF-36 emotional well-being at week 12, mean |
| End point description:<br>Mean SF-36 emotional well-being at week 12 |                                             |
| End point type                                                       | Secondary                                   |
| End point timeframe:<br>week 12                                      |                                             |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 72.2 (± 18.8)                    | 59.2 (± 24.9)                   | 66.5 (± 21.1)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 emotional well-being at week 24, mean

|                        |                                             |
|------------------------|---------------------------------------------|
| End point title        | SF-36 emotional well-being at week 24, mean |
| End point description: | Mean SF-36 emotional well-being at week 24  |
| End point type         | Secondary                                   |
| End point timeframe:   | week 24                                     |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 38                               | 28                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 73.8 (± 18.7)                    | 65.4 (± 19.1)                   | 72.6 (± 18.7)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DAS28 at week 24, median

|                        |                          |
|------------------------|--------------------------|
| End point title        | DAS28 at week 24, median |
| End point description: | Median DAS28 at week 24  |
| End point type         | Secondary                |
| End point timeframe:   | week 24                  |

| End point values                      | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|---------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                    | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed           | 34                               | 32                              | 39                                          |  |
| Units: AU                             |                                  |                                 |                                             |  |
| median (inter-quartile range (Q1-Q3)) | 2.43 (1.86 to 3.84)              | 2.89 (2.20 to 3.82)             | 3.34 (2.76 to 4.11)                         |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 energy/fatigue at week 12, mean

|                        |                                       |
|------------------------|---------------------------------------|
| End point title        | SF-36 energy/fatigue at week 12, mean |
| End point description: | Mean SF-36 energy/fatigue at week 12  |
| End point type         | Secondary                             |
| End point timeframe:   | week 12                               |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 54.1 (± 22.3)                    | 45.9 (± 24.7)                   | 54.9 (± 22.9)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 energy/fatigue at week 24, mean

|                        |                                       |
|------------------------|---------------------------------------|
| End point title        | SF-36 energy/fatigue at week 24, mean |
| End point description: | Mean SF-36 energy/fatigue at week 24  |
| End point type         | Secondary                             |
| End point timeframe:   | week 24                               |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 58.2 (± 22.6)                    | 51.4 (± 19.3)                   | 63.1 (± 19.6)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 general health at week 12, mean

|                                      |                                       |
|--------------------------------------|---------------------------------------|
| End point title                      | SF-36 general health at week 12, mean |
| End point description:               |                                       |
| Mean SF-36 general health at week 12 |                                       |
| End point type                       | Secondary                             |
| End point timeframe:                 |                                       |
| week 12                              |                                       |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 53.5 (± 15.6)                    | 47.9 (± 21.4)                   | 50.6 (± 16.3)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 general health at week 24, mean

|                                      |                                       |
|--------------------------------------|---------------------------------------|
| End point title                      | SF-36 general health at week 24, mean |
| End point description:               |                                       |
| Mean SF-36 general health at week 24 |                                       |
| End point type                       | Secondary                             |
| End point timeframe:                 |                                       |
| week 24                              |                                       |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 59.9 (± 16.0)                    | 51.7 (± 15.4)                   | 52.5 (± 14.7)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 health change at week 12, mean

|                                     |                                      |
|-------------------------------------|--------------------------------------|
| End point title                     | SF-36 health change at week 12, mean |
| End point description:              |                                      |
| Mean SF-36 health change at week 12 |                                      |
| End point type                      | Secondary                            |
| End point timeframe:                |                                      |
| week 12                             |                                      |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 76.8 (± 27.3)                    | 64.0 (± 27.4)                   | 60.2 (± 27.7)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 health change at week 24, mean

|                                     |                                      |
|-------------------------------------|--------------------------------------|
| End point title                     | SF-36 health change at week 24, mean |
| End point description:              |                                      |
| Mean SF-36 health change at week 24 |                                      |
| End point type                      | Secondary                            |
| End point timeframe:                |                                      |
| week 24                             |                                      |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 84.6 (± 23.0)                    | 68.0 (± 28.6)                   | 73.7 (± 25.6)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 pain at week 12, mean

|                        |                             |
|------------------------|-----------------------------|
| End point title        | SF-36 pain at week 12, mean |
| End point description: | Mean SF-36 pain at week 12  |
| End point type         | Secondary                   |
| End point timeframe:   | week 12                     |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 63.9 (± 21.8)                    | 50.1 (± 24.1)                   | 53.2 (± 20.4)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 pain at week 24, mean

|                        |                             |
|------------------------|-----------------------------|
| End point title        | SF-36 pain at week 24, mean |
| End point description: | Mean SF-36 pain at week 24  |
| End point type         | Secondary                   |
| End point timeframe:   | week 24                     |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 67.1 (± 21.4)                    | 59.5 (± 24.2)                   | 63.5 (± 22.5)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 physical functioning at week 12, mean

|                        |                                             |
|------------------------|---------------------------------------------|
| End point title        | SF-36 physical functioning at week 12, mean |
| End point description: | Mean SF-36 physical functioning at week 12  |
| End point type         | Secondary                                   |
| End point timeframe:   | week 12                                     |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 69.4 (± 22.4)                    | 53.8 (± 27.5)                   | 67.9 (± 24.6)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 physical functioning at week 24, mean

|                        |                                             |
|------------------------|---------------------------------------------|
| End point title        | SF-36 physical functioning at week 24, mean |
| End point description: | Mean SF-36 physical functioning at week 24  |
| End point type         | Secondary                                   |
| End point timeframe:   | week 24                                     |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 72.8 (± 21.5)                    | 63.6 (± 26.5)                   | 69.2 (± 25.7)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DAS28 at week 12, median

|                        |                          |
|------------------------|--------------------------|
| End point title        | DAS28 at week 12, median |
| End point description: | Median DAS28 at week 12  |
| End point type         | Secondary                |
| End point timeframe:   | week 12                  |

| End point values                      | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|---------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                    | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed           | 48                               | 40                              | 46                                          |  |
| Units: AU                             |                                  |                                 |                                             |  |
| median (inter-quartile range (Q1-Q3)) | 3.1 (2.35 to 3.85)               | 3.29 (2.79 to 4.19)             | 3.71 (3.01 to 4.33)                         |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: BOLD signal at week 12, mean

|                        |                              |
|------------------------|------------------------------|
| End point title        | BOLD signal at week 12, mean |
| End point description: | Mean BOLD signal at week 12  |
| End point type         | Secondary                    |
| End point timeframe:   | week 12                      |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 48                               | 40                              | 46                                          |  |
| Units: cm3                           |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 2364 (± 3756.80)                 | 1376.08 (± 2362.60)             | 1395.15 (± 2325.67)                         |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: BOLD signal at week 24, mean

|                             |                              |
|-----------------------------|------------------------------|
| End point title             | BOLD signal at week 24, mean |
| End point description:      |                              |
| Mean BOLD signal at week 24 |                              |
| End point type              | Secondary                    |
| End point timeframe:        |                              |
| week 24                     |                              |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 38                               | 28                              | 39                                          |  |
| Units: 12872.02                      |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 1787.13 (± 2487.46)              | 1102.62 (± 1665.20)             | 1934.03 (± 3976.96)                         |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: BOLD signal at week 12, median

|                               |                                |
|-------------------------------|--------------------------------|
| End point title               | BOLD signal at week 12, median |
| End point description:        |                                |
| Median BOLD signal at week 12 |                                |
| End point type                | Secondary                      |
| End point timeframe:          |                                |
| week 12                       |                                |

| End point values            | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|-----------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type          | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed | 48                               | 38                              | 46                                          |  |
| Units: voxel                | 48                               | 38                              | 46                                          |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: BOLD signal at week 24, median

|                               |                                |
|-------------------------------|--------------------------------|
| End point title               | BOLD signal at week 24, median |
| End point description:        |                                |
| Median BOLD signal at week 24 |                                |
| End point type                | Secondary                      |
| End point timeframe:          |                                |
| week 24                       |                                |

| End point values                      | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|---------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                    | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed           | 38                               | 28                              | 39                                          |  |
| Units: 2446.00                        |                                  |                                 |                                             |  |
| median (inter-quartile range (Q1-Q3)) | 824.76 (241.50 to 1625.17)       | 707.56 (76.44 to 1477.28)       | 327 (26.67 to 3175.25)                      |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 role limitation physical at week 12, mean

|                                                |                                                 |
|------------------------------------------------|-------------------------------------------------|
| End point title                                | SF-36 role limitation physical at week 12, mean |
| End point description:                         |                                                 |
| Mean SF-36 role limitation physical at week 12 |                                                 |
| End point type                                 | Secondary                                       |
| End point timeframe:                           |                                                 |
| week 12                                        |                                                 |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 50.0 (± 41.8)                    | 38.9 (± 46.5)                   | 48.1 (± 44.4)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 role limitation physical at week 24, mean

|                        |                                                 |
|------------------------|-------------------------------------------------|
| End point title        | SF-36 role limitation physical at week 24, mean |
| End point description: | Mean SF-36 role limitation physical at week 24  |
| End point type         | Secondary                                       |
| End point timeframe:   | week 24                                         |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 59.6 (± 42.3)                    | 52.7 (± 43.7)                   | 63.2 (± 40.3)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 social functioning at week 12, mean

|                        |                                           |
|------------------------|-------------------------------------------|
| End point title        | SF-36 social functioning at week 12, mean |
| End point description: | Mean SF-36 social functioning at week 12  |
| End point type         | Secondary                                 |
| End point timeframe:   | week 12                                   |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 83.9 (± 21.4)                    | 67.2 (± 29.6)                   | 79.3 (± 21.7)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 social functioning at week 24, mean

|                        |                                           |
|------------------------|-------------------------------------------|
| End point title        | SF-36 social functioning at week 24, mean |
| End point description: |                                           |
| End point type         | Secondary                                 |
| End point timeframe:   |                                           |
| week 24                |                                           |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 84.9 (± 19.2)                    | 80.5 (± 22.4)                   | 84.6 (± 20.0)                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF-36 role limitation emotional at week 12, mean

|                                                 |                                                  |
|-------------------------------------------------|--------------------------------------------------|
| End point title                                 | SF-36 role limitation emotional at week 12, mean |
| End point description:                          |                                                  |
| Mean SF-36 role limitation emotional at week 12 |                                                  |
| End point type                                  | Secondary                                        |
| End point timeframe:                            |                                                  |
| week 12                                         |                                                  |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 42                               | 46                              | 46                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 71.4 (± 37.2)                    | 47.6 (± 45.5)                   | 62.0 (± 41.5)                               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: SF-36 role limitation emotional at week 24, mean

|                        |                                                  |
|------------------------|--------------------------------------------------|
| End point title        | SF-36 role limitation emotional at week 24, mean |
| End point description: | Mean SF-36 role limitation emotional at week 24  |
| End point type         | Secondary                                        |
| End point timeframe:   | week 24                                          |

| End point values                     | Group 1 (high voxel count + CZP) | Group 2 (low voxel count + CZP) | Group 3 (high or low voxel count + placebo) |  |
|--------------------------------------|----------------------------------|---------------------------------|---------------------------------------------|--|
| Subject group type                   | Reporting group                  | Reporting group                 | Reporting group                             |  |
| Number of subjects analysed          | 34                               | 32                              | 39                                          |  |
| Units: AU                            |                                  |                                 |                                             |  |
| arithmetic mean (standard deviation) | 72.5 (± 37.1)                    | 57.0 (± 44.0)                   | 66.7 (± 41.2)                               |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Enrollment (signature ICF) until week 24 (visit 6)

Adverse event reporting additional description:

All physical examination findings, vital sign abnormalities, clinical laboratory abnormalities, and ECG changes will be captured as AEs when deemed medically significant by the investigator. Adverse events will be assessed during all visits except Visit 1.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 24 |
|--------------------|----|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Randomized patients |
|-----------------------|---------------------|

Reporting group description: -

| Serious adverse events                                              | Randomized patients |  |  |
|---------------------------------------------------------------------|---------------------|--|--|
| Total subjects affected by serious adverse events                   |                     |  |  |
| subjects affected / exposed                                         | 6 / 138 (4.35%)     |  |  |
| number of deaths (all causes)                                       | 0                   |  |  |
| number of deaths resulting from adverse events                      | 0                   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |  |  |
| Tongue neoplasm                                                     |                     |  |  |
| subjects affected / exposed                                         | 1 / 138 (0.72%)     |  |  |
| occurrences causally related to treatment / all                     | 1 / 1               |  |  |
| deaths causally related to treatment / all                          | 0 / 0               |  |  |
| Injury, poisoning and procedural complications                      |                     |  |  |
| Pelvic fracture                                                     |                     |  |  |
| subjects affected / exposed                                         | 1 / 138 (0.72%)     |  |  |
| occurrences causally related to treatment / all                     | 0 / 1               |  |  |
| deaths causally related to treatment / all                          | 0 / 0               |  |  |
| Surgical and medical procedures                                     |                     |  |  |
| Coronary arterial stent insertion                                   |                     |  |  |
| subjects affected / exposed                                         | 1 / 138 (0.72%)     |  |  |
| occurrences causally related to treatment / all                     | 0 / 1               |  |  |
| deaths causally related to treatment / all                          | 0 / 0               |  |  |
| Immune system disorders                                             |                     |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Anaphylactic reaction                           |                 |  |  |
| subjects affected / exposed                     | 1 / 138 (0.72%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Otitis media chronic                            |                 |  |  |
| subjects affected / exposed                     | 1 / 138 (0.72%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 138 (0.72%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

Frequency threshold for reporting non-serious adverse events: 2.5 %

| <b>Non-serious adverse events</b>                     | Randomized patients |  |  |
|-------------------------------------------------------|---------------------|--|--|
| Total subjects affected by non-serious adverse events |                     |  |  |
| subjects affected / exposed                           | 72 / 138 (52.17%)   |  |  |
| Nervous system disorders                              |                     |  |  |
| Headache                                              |                     |  |  |
| subjects affected / exposed                           | 5 / 138 (3.62%)     |  |  |
| occurrences (all)                                     | 5                   |  |  |
| Hypoaesthesia                                         |                     |  |  |
| subjects affected / exposed                           | 1 / 138 (0.72%)     |  |  |
| occurrences (all)                                     | 3                   |  |  |
| General disorders and administration site conditions  |                     |  |  |
| Influenza like illness                                |                     |  |  |
| subjects affected / exposed                           | 3 / 138 (2.17%)     |  |  |
| occurrences (all)                                     | 5                   |  |  |
| Injection site reaction                               |                     |  |  |
| subjects affected / exposed                           | 2 / 138 (1.45%)     |  |  |
| occurrences (all)                                     | 4                   |  |  |
| Fatigue                                               |                     |  |  |

|                                                  |                      |  |  |
|--------------------------------------------------|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 3 / 138 (2.17%)<br>3 |  |  |
| Gastrointestinal disorders                       |                      |  |  |
| Diarrhoea                                        |                      |  |  |
| subjects affected / exposed                      | 6 / 138 (4.35%)      |  |  |
| occurrences (all)                                | 7                    |  |  |
| nausea                                           |                      |  |  |
| subjects affected / exposed                      | 3 / 138 (2.17%)      |  |  |
| occurrences (all)                                | 3                    |  |  |
| Respiratory, thoracic and mediastinal disorders  |                      |  |  |
| Cough                                            |                      |  |  |
| subjects affected / exposed                      | 2 / 138 (1.45%)      |  |  |
| occurrences (all)                                | 3                    |  |  |
| Skin and subcutaneous tissue disorders           |                      |  |  |
| Rash                                             |                      |  |  |
| subjects affected / exposed                      | 3 / 138 (2.17%)      |  |  |
| occurrences (all)                                | 4                    |  |  |
| Pruritus                                         |                      |  |  |
| subjects affected / exposed                      | 2 / 138 (1.45%)      |  |  |
| occurrences (all)                                | 3                    |  |  |
| Musculoskeletal and connective tissue disorders  |                      |  |  |
| Back pain                                        |                      |  |  |
| subjects affected / exposed                      | 2 / 138 (1.45%)      |  |  |
| occurrences (all)                                | 4                    |  |  |
| Infections and infestations                      |                      |  |  |
| Nasopharyngitis                                  |                      |  |  |
| subjects affected / exposed                      | 28 / 138 (20.29%)    |  |  |
| occurrences (all)                                | 40                   |  |  |
| Oral herpes                                      |                      |  |  |
| subjects affected / exposed                      | 4 / 138 (2.90%)      |  |  |
| occurrences (all)                                | 4                    |  |  |
| Respiratory tract infection                      |                      |  |  |
| subjects affected / exposed                      | 3 / 138 (2.17%)      |  |  |
| occurrences (all)                                | 7                    |  |  |
| Upper respiratory tract infection                |                      |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 138 (1.45%) |  |  |
| occurrences (all)           | 3               |  |  |
| Urinary tract infection     |                 |  |  |
| subjects affected / exposed | 3 / 138 (2.17%) |  |  |
| occurrences (all)           | 5               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                           |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 05 April 2013     | Changes were made due to the deficiency letter of the local ethic.                                                                                                                                                                                                                                                                                  |
| 17 December 2013  | <ul style="list-style-type: none"><li>-Additional lab sample for RF/anti-CCP has been added</li><li>- WOMAC score has been deleted</li><li>- 2 new sides have been added</li></ul>                                                                                                                                                                  |
| 02 May 2014       | <ul style="list-style-type: none"><li>- change of address of study aDMINISTRATION</li><li>- more detailed explanation in the study synopsis has been made (page 8)</li><li>- correct numeration in "table of contents have been made"</li><li>- changes in "schedule of assessments" have been made</li><li>- another side has been added</li></ul> |
| 10 December 2014  | Due to the addition of new countries several changes were needed to harmonize different requirements of each country and to explain things in more detail.                                                                                                                                                                                          |
| 17 November 2015  | <ul style="list-style-type: none"><li>- changes of wording have been made</li></ul>                                                                                                                                                                                                                                                                 |
| 10 March 2017     | <ul style="list-style-type: none"><li>- wording has been changed.</li><li>- table of contents have been adapted</li><li>- figure has been changed for consistency</li><li>- -detailed explanation of treatment diagram has been addeed</li><li>- address for SAE reporting has been changed</li></ul>                                               |
| 19 July 2017      | <ul style="list-style-type: none"><li>-wording has been changed</li><li>- change of Subject infomration "Cimzia"</li></ul>                                                                                                                                                                                                                          |
| 21 September 2017 | <ul style="list-style-type: none"><li>- wording has been changed</li><li>- change of Principle investigator Erlangen</li></ul>                                                                                                                                                                                                                      |
| 12 November 2017  | <ul style="list-style-type: none"><li>- change in study administration</li><li>- wording has been changed</li></ul>                                                                                                                                                                                                                                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported