EU Clinical Trials Register

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
Scientific contact	Clinical Trial Unit, Med. 3 , Universitätsklinikum Erlangen, +49 91318543014, juergen.rech@uk-erlangen.de

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, heamatocrit, 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 somatosensoric 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 α antagonists represents a major advance in the drug treatment of RA. The therapeutic response to currently available TNF α 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 α antagonists for the treatment of RA.
The benefit of the protocol PreCePra are the potential future a availability of a predictor before treating

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

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	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:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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 met 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
Arm title	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.

Arm title	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.

Arm title	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
Arm title	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.

Arm title	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.

Arm title	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
Arm title	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.

Arm title	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.

Arm title	Group 3 (high or low voxel count + placebo)

Arm description:

fMRI: high or low voxel Count; randomized to : placobo; 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:	
fMRI: high voxel count; randomized to: Certolizumab Pegol	
Reporting group title	Group 2 (low voxel count + CZP)
Reporting group description:	
fMRI: low voxel Count; randomized to: Certolizumab Pegol	
Reporting group title	Group 3 (high or low voxel count + placebo)
Reporting group description:	
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 ≥ 18 years at time of consent			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	54.3	56.5	52.1
standard deviation	± 10.8	± 12.2	± 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

Reporting group values	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 (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female Male	108 48		
ACPA Units: Subjects			
positive negative	114 42		
RF Units: Subjects			
positive negative	109 47		

Tender joints (28)
Units: joints
    arithmetic mean
    standard deviation
	
	-		

Swollen joints
Units: joints
    arithmetic mean
    standard deviation
	
	-		

Patient global VAS
Units: mm
    arithmetic mean
    standard deviation
	
	-		

Physician global VAS
Units: mm
    arithmetic mean
    standard deviation
	
	-		

Pain VAS
Units: mm
    arithmetic mean
    standard deviation
	
	-		

ESR
Units: mm/h
    arithmetic mean
    standard deviation
	
	-		

CRP
Units: mg/l
    arithmetic mean
    standard deviation
	
	-		

DAS28
Units: none
    arithmetic mean
    standard deviation
	
	-		

End points

End points reporting groups

Reporting group title	Group 1 (high voxel count + CZP)
Reporting group description:	
fMRI: high voxel count; randomized to: Certolizumab Pegol	
Reporting group title	Group 2 (low voxel count + CZP)
Reporting group description:	
fMRI: low voxel Count; randomized to: Certolizumab Pegol	
Reporting group title	Group 3 (high or low voxel count + placebo)
Reporting group description:	
fMRI: high or low voxel Count; randomized to: placebo	
Reporting group title	Group 1 (high voxel count + CZP)
Reporting group description:	
fMRI: high voxel Count; randomized to: Certolizumab Pegol	
Reporting group title	Group 2 (low voxel count + CZP)
Reporting group description:	
fMRI: low voxel Count; randomized to: Certolizumab Pegol	
Reporting group title	Group 3 (high or low voxel count + placebo)
Reporting group description:	
fMRI: high or low voxel Count; randomized to: placebo	
Reporting group title	Group 1 (high voxel count + CZP)
Reporting group description:	
fMRI: high voxel Count; randomized to : Certolizumab Pegol; responder at week 12	
Reporting group title	Group 2 (low voxel count + CZP)
Reporting group description:	
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:	
fMRI: high or low voxel Count; randomized to : placobo; 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:	
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:	
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:	
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:	
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:	
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

Statistical analysis title	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[1]
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[2]
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:	
Mean 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				
arithmetic mean (standard deviation)	2.79 (± 1.11)	3.2 (± 1.11)	3.11 (± 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:	
Mean SF-36 emotional well-being 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)	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 %

Non-serious adverse events	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	3 / 138 (2.17%)		
occurrences (all)	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	-Additional lab sample for RF/anti-CCP has been added - WOMAC score has been deleted - 2 new sides have been added
02 May 2014	- change of address of study aDMINISTRATION - more detailed explanation in the study synopsis has been made (page 8) - correct numeration in "table of contents have been made" - changes in "schedule of assessments" have been made - another side has been added
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	- changes of wording have been made
10 March 2017	- wording has been changed. - table of contents have been adapted - figure has been changed for consistency - -detailed explanation of treatment diagram has been addeed - address for SAE reporting has been changed
19 July 2017	-wording has been changed - change of Subject infomration "Cimzia"
21 September 2017	- wording has been changed - change of Principle investigator Erlangen
12 November 2017	- change in study administration - wording has been changed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported