Clinical trial results:
Phase 3, Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Certolizumab Pegol in Subjects With Adult-Onset Active and Progressive Psoriatic Arthritis (PsA)

Summary

EudraCT number	2009-011720-59
Trial protocol	FR DE ES GB BE HU NL CZ IE IT
Global end of trial date	24 August 2015

Results information

Result version number	v1 (current)
This version publication date	08 September 2016
First version publication date	08 September 2016

Trial information

Trial identification

Sponsor protocol code	PsA001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01087788
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES GmbH
Sponsor organisation address	Alfred-Nobel-Strasse 10, Monheim, Germany, 40789
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final

Date of interim/final analysis	13 April 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of Certolizumab pegol (CZP) administered sc at the dose of 200mg every two weeks (Q2W) or 400mg every four weeks (Q4W) after loading with 400mg at Weeks 0, 2, and 4 on the signs and symptoms of active psoriatic arthritis (PsA) and on the inhibition of progression of structural damage in adults with active PsA

Protection of trial subjects:

Not applicable

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	02 March 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 84
Country: Number of subjects enrolled	Argentina: 50
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Czech Republic: 67
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Poland: 101
Worldwide total number of subjects	409
EEA total number of subjects	251

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)	383
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll patients in March 2010 and concluded in August 2015.

Pre-assignment

Screening details:

The study included a 24-week Double-Blind, a 24-week Dose-Blind, and an Open-Label Treatment Period.
409 subjects are included in Randomized Set (RS) shown in the Participant Flow, which is an Intention-to- Treat (ITT) dataset.

Period 1

Period 1 title	24-weeks Double-blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group and were re-randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arm on Week 16.

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

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections every 2 Weeks or every 4 Weeks

Arm title	CZP 200 mg Q2W

Arm description:

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

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

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	Certolizumab pegol
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or 400 mg every 4 Weeks

Arm title	CZP 400 mg Q4W

Arm description:

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

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

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	Certolizumab pegol
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or 400 mg every 4 Weeks

Number of subjects in period 1	Placebo	CZP 200 mg Q2W	CZP 400 mg Q4W
Started	136	138	135
Completed	120	128	120
Not completed	16	10	15
AE, unknown type	-	-	1
Protocol deviation	-	1	-
Lack of efficacy	2	-	1
Other reason	1	2	1
AE, serious fatal	-	1	1
AE, non-serious non-fatal	2	1	2
Consent withdrawn by subject	7	2	5
AE, serious non-fatal	-	2	3
Lost to follow-up	4	1	1

Period 2

Period 2 title	24-weeks Double-blind Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Assessor, Carer, Investigator, Subject

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo

Arm description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group and were re-randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arm on Week 16.

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

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections every 2 Weeks or every 4 Weeks

Arm title	CZP 200 mg Q2W

Arm description:

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

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

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	Certolizumab pegol
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or 400 mg every 4 Weeks

Arm title	CZP 400 mg Q4W

Arm description:

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

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

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	Certolizumab pegol
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or 400 mg every 4 Weeks

Number of subjects in period 2	Placebo	CZP 200 mg Q2W	CZP 400 mg Q4W
Started	120	128	120
Completed	113	123	114
Not completed	7	5	6
Lack of efficacy	-	2	1
AE, serious fatal	-	1	-
AE, non-serious non-fatal	2	1	1
Consent withdrawn by subject	1	-	-
AE, serious non-fatal	2	1	2
other	1	-	1
Lost to follow-up	1	-	1

Period 3

Period 3 title	Open-Label Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group and were re-randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arm on Week 16.

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

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections every 2 Weeks or every 4 Weeks

Arm title	CZP 200 mg Q2W

Arm description:

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

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

Arm type	Experimental

Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	Certolizumab pegol
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or 400 mg every 4 Weeks

Arm title	CZP 400 mg Q4W

Arm description:

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

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

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	Certolizumab pegol
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg every 2 Weeks or 400 mg every 4 Weeks

Number of subjects in period 3[1]	Placebo	CZP 200 mg Q2W	CZP 400 mg Q4W
Started	111	121	114
Completed	81	97	86
Not completed	30	24	28
Protocol deviation	2	1	-
AE, non-serious unknown	1	-	-
Lack of efficacy	4	2	3
AE, serious fatal	2	-	1
SAE, non-fatal+AE, non-serious non-fatal	-	1	-
AE, non-serious non-fatal	6	4	4
Consent withdrawn by subject	13	8	10
AE, serious non-fatal	1	3	4
other	1	1	4
Lost to follow-up	-	4	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 4 subjects completed the Dose-Blind Period and then withdrew from the study rather than entering the Open-Label Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group and were re-randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arm on Week 16.

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

Reporting group title	CZP 200 mg Q2W

Reporting group description:

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

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

Reporting group title	CZP 400 mg Q4W

Reporting group description:

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

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

Reporting group values	Placebo	CZP 200 mg Q2W	CZP 400 mg Q4W
Number of subjects	136	138	135
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	129	126	128
>=65 years	7	12	7
Age Continuous Units: years			
arithmetic mean	47.3	48.2	47.1
standard deviation	± 11.1	± 12.3	± 10.8
Gender Categorical Units: Subjects			
Female	79	74	73
Male	57	64	62

Reporting group values	Total		
Number of subjects	409		
Age Categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	383		
>=65 years	26		
Age Continuous Units: years			
arithmetic mean			

standard deviation	-		

Gender Categorical Units: Subjects			
Female	226		
Male	183		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group and were re-randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arm on Week 16.

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

Reporting group title	CZP 200 mg Q2W

Reporting group description:

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

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

Reporting group title	CZP 400 mg Q4W

Reporting group description:

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

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

Reporting group title	Placebo

Reporting group description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group and were re-randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arm on Week 16.

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

Reporting group title	CZP 200 mg Q2W

Reporting group description:

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

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

Reporting group title	CZP 400 mg Q4W

Reporting group description:

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

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

Reporting group title	Placebo

Reporting group description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group and were re-randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arm on Week 16.

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

Reporting group title	CZP 200 mg Q2W

Reporting group description:

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

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

Reporting group title	CZP 400 mg Q4W

Reporting group description:

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

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

Subject analysis set title	All CZP 200 mg Q2W
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes all subjects who were randomized to CZP 200 mg Q2W at Baseline and those subjects who escaped or were re-randomized from Placebo to CZP 200 mg Q2W.

Subjects received one injection of 200 mg CZP and one injection of Placebo every two weeks to maintain the study blind.

Subject analysis set title	All CZP 400 mg Q4W
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes all subjects who were randomized to CZP 400 mg Q4W at Baseline and those subjects who escaped or were re-randomized from Placebo to CZP 400 mg Q4W.

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

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

Subject analysis set description:

This arm shows all patients treated with Certolizumab Pegol (CZP) at least once. Hence, this arm is a combination of arm All CZP 200 mg Q2W and arm All CZP 400 mg Q4W.

Subject analysis set title	Placebo (Randomized Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Matching Placebo to Certolizumab Pegol (CZP) injections from Week 0 to Week 24. Placebo subjects who did not achieve certain predefined response criteria at both Weeks 14 and 16 left the Placebo group and were re-randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arm on Week 16.

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

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

Subject analysis set description:

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

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

Subject analysis set title	CZP 400 mg Q4W (Randomized Set)
Subject analysis set type	Full analysis

Subject analysis set description:

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

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

Subject analysis set title	CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Subject analysis set type	Full analysis

Subject analysis set description:

This combined group includes subjects of the two treatment arms CZP 200 mg Q2W and CZP 400 mg Q4W used in some analyses.

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

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

Primary: American College of Rheumatology 20 (ACR20) response at Week 12

End point title	American College of Rheumatology 20 (ACR20) response at Week 12

End point description:

ACR20 responders are those subjects with at least 20 % improvement from Baseline for Tender Joint Count (TJC), Swollen Joint Count (SJC), and at least 3 of the 5 remaining core set measures: 1) Health Assessment Questionnaire-Disability Index (HAQ-DI), 2) C-reactive Protein (CRP), 3) Patient's Assessment of Arthritis Pain-Visual Analog Scale (PAAP-VAS), 4) Patient's Global Assessment of Disease Activity-Visual Analog Scale (PtGADA-VAS), 5) Physician's Global Assessment of Disease Activity-Visual Analog Scale (PhGADA-VAS).

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo (Randomized Set)	CZP 200 mg Q2W (Randomized Set)	CZP 400 mg Q4W (Randomized Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	136	138	135	
Units: percentage of participants				
number (confidence interval 95%)				
Percentage of participants	24.3 (17.1 to 31.5)	58 (49.7 to 66.2)	51.9 (43.4 to 60.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 200 mg Q2W (Randomized Set)
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [1]
Method	Wald-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	33.7
Confidence interval	
level	95 %
sides	2-sided

lower limit	22.8
upper limit	44.6

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 400 mg Q4W (Randomized Set)
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [2]
Method	Wald-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	27.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.5
upper limit	38.7

Notes:

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

Primary: Change from Baseline in modified Total Sharp Score (mTSS) in modification for Psoriatic Arthritis at Week 24

End point title	Change from Baseline in modified Total Sharp Score (mTSS) in modification for Psoriatic Arthritis at Week 24

End point description:

Van der Heijde modified Total Sharp Score (mTSS) is a methodology to assess the degree of joint damage by quantifying the extent of bone erosions and joint space narrowing for 64 and 52 joints, respectively, with higher scores representing greater damage. mTSS (bone erosions) ranges from 0 (best possible outcome) to 320 (worst possible outcome); mTSS (joint space narrowing) ranges from 0 (best possible outcome) to 208 (worst possible outcome); and total score ranges from 0 (best possible outcome) to 528 (worst possible outcome). For the pre-defined analysis of this outcome measure, 0 was used for Baseline and the maximum observed mTSS value was used for Week 24 for those subjects which had less than 2 radiographs. The re-analysis is restricted to those subjects in the Randomized Set who have at least 2 x-ray values at scheduled visits, which are at least 8 weeks apart.

End point type	Primary

End point timeframe:

From Baseline to Week 24

End point values	Placebo (Randomized Set)	CZP 200 mg Q2W (Randomized Set)	CZP 400 mg Q4W (Randomized Set)	CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	136	138	135	273
Units: units on a scale				
least squares mean (confidence interval 95%)				
Pre-defined results	28.92 (13.73 to 44.11)	11.52 (-3.4 to 26.45)	25.05 (9.48 to 40.61)	18.28 (6.34 to 30.23)
Re-analysis results (n = 123, 130, 123, 253)	0.18 (0.04 to 0.33)	-0.02 (-0.16 to 0.11)	0.09 (-0.05 to 0.23)	0.03 (-0.08 to 0.14)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.203 [3]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-10.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.05
upper limit	5.77
Variability estimate	Standard error of the mean
Dispersion value	8.35

Notes:

[3] - Difference of CZP 200 mg + 400 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using an ANCOVA model with treatment, region and prior TNF-antagonist exposure as factors and Baseline mTSS score as a covariate.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 200 mg Q2W (Randomized Set)
Number of subjects included in analysis	274
Analysis specification	Pre-specified

Analysis type	
P-value	= 0.017 [4]
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[4] - Difference of CZP 200 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using an ANCOVA model with treatment, region and prior TNF-antagonist exposure as factors and Baseline mTSS score as a covariate.

Secondary: American College of Rheumatology 20 (ACR20) response at Week 24

End point title	American College of Rheumatology 20 (ACR20) response at Week 24

End point description:

ACR20 responders are those subjects with at least 20 % improvement from Baseline for Tender Joint Count (TJC), Swollen Joint Count (SJC), and at least 3 of the 5 remaining core set measures: 1) Health Assessment Questionnaire-Disability Index (HAQ-DI), 2) C-reactive Protein (CRP), 3) Patient's Assessment of Arthritis Pain-Visual Analog Scale (PAAP-VAS), 4) Patient's Global Assessment of Disease Activity-Visual Analog Scale (PtGADA-VAS), 5) Physician's Global Assessment of Disease Activity-Visual Analog Scale (PhGADA-VAS).

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo (Randomized Set)	CZP 200 mg Q2W (Randomized Set)	CZP 400 mg Q4W (Randomized Set)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	136	138	135	
Units: percentage of participants				
number (confidence interval 95%)				
percentage of participants	23.5 (16.4 to 30.7)	63.8 (55.7 to 71.8)	56.3 (47.9 to 64.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 200 mg Q2W (Randomized

	Set)
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [5]
Method	Wald-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	40.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.5
upper limit	51

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 400 mg Q4W (Randomized Set)
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [6]
Method	Wald-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	32.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.8
upper limit	43.8

Notes:

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

Secondary: Change from Baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI) at Week 24

End point title	Change from Baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI) at Week 24

End point description:

The HAQ-DI is a measure of function in Arthritis. There are 20 items in eight categories that represent a comprehensive set of functional activities on a scale from 0 (without difficulty) to 3 (unable to perform without assistance). The category scores are averaged into an overall HAQ-DI from 0 to 3. Scores of 0 to 1 generally represent mild to moderate difficulty, 1 to 2 represent moderate to severe disability, and 2 to 3 indicate severe to very severe disability. A negative value in HAQ-DI change from Baseline indicates an improvement from Baseline. The higher the negative value, the higher the improvement.

End point type	Secondary

End point timeframe:

End point values	Placebo (Randomized Set)	CZP 200 mg Q2W (Randomized Set)	CZP 400 mg Q4W (Randomized Set)	CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	136	138	135	273
Units: units on a scale				
least squares mean (confidence interval 95%)				
units on a scale	-0.19 (-0.29 to -0.09)	-0.54 (-0.64 to -0.44)	-0.46 (-0.56 to -0.36)	-0.5 (-0.58 to -0.42)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[7] - Difference of CZP 200 mg + 400 mg vs. Placebo (and corresponding 95 % Confidence Interval and pvalue) were estimated using an ANCOVA model with treatment, region and prior TNF-antagonist exposure as factors and Baseline HAQ-DI score as a covariate.

Secondary: Psoriasis Area Severity Index (PASI75) response at Week 24 in the subgroup of subjects with Psoriasis (PSO) involving at least 3 % Body Surface Area (BSA) at Baseline

End point title	Psoriasis Area Severity Index (PASI75) response at Week 24 in the subgroup of subjects with Psoriasis (PSO) involving at least 3 % Body Surface Area (BSA) at Baseline

End point description:

The PASI75 response assessments are based on at least 75 % improvement in the PASI score from Baseline. The PASI score is a measure of the average redness, thickness, and scaliness of the psoriatic skin lesions (each graded on a 0 to 4 scale), weighted by the area of involvement.

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo (Randomized Set)	CZP 200 mg Q2W (Randomized Set)	CZP 400 mg Q4W (Randomized Set)	CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	86	90	76	166
Units: percentage of participants				
number (confidence interval 95%)				
percentage of participants	15.1 (7.5 to 22.7)	62.2 (52.2 to 72.2)	60.5 (49.5 to 71.5)	61.4 (54 to 68.8)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [8]
Method	Wald-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	46.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.7
upper limit	56.9

Notes:

[8] - Difference of Certolizumab Pegol 200 mg + 400 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using a standard two-sided Wald asymptotic test with a 5 % alpha level.

Secondary: Change From Baseline in Modified Total Sharp Score (mTSS) at Week 48

End point title	Change From Baseline in Modified Total Sharp Score (mTSS) at Week 48

End point description:

Van der Heijde modified Total Sharp Score (mTSS) is a methodology to assess the degree of joint

damage by quantifying the extent of bone erosions and joint space narrowing for 64 and 52 joints, respectively, with higher scores representing greater damage. mTSS (bone erosions) ranges from 0 (best possible outcome) to 320 (worst possible outcome); mTSS (joint space narrowing) ranges from 0 (best possible outcome) to 208 (worst possible outcome); and total score ranges from 0 (best possible outcome) to 528 (worst possible outcome).
For the analysis of this outcome measure, the change from Baseline to Week 48 was imputed using the median change from Baseline among all subjects for those subjects, which had less than 2 radiographs. The post-hoc analysis presented here is based on the subgroup of subjects which had a Baseline mTSS value greater than 6.

End point type	Secondary

End point timeframe:

From Baseline to Week 48

End point values	Placebo (Randomized Set)	CZP 200 mg Q2W (Randomized Set)	CZP 400 mg Q4W (Randomized Set)	CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	136	138	135	273
Units: units on a scale				
least squares mean (confidence interval 95%)				
Predefined results: Overall	0.32 (0.1 to 0.55)	0.15 (-0.07 to 0.37)	0.11 (-0.12 to 0.34)	0.13 (-0.05 to 0.31)
Post-hoc results: Basel. mTSS > 6 (n=61,65,65,130)	0.78 (0.31 to 1.25)	0.31 (-0.15 to 0.77)	0.22 (-0.24 to 0.67)	0.26 (-0.09 to 0.62)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	Placebo (Randomized Set) v CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.127 [9]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[9] - Difference of CZP 200 mg + 400 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using an ANCOVA model with treatment, region and prior TNF-antagonist exposure as factors and Baseline mTSS score as a covariate.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. Conditional on the first test being significant, the second hypothesis was tested with the same alpha level of 5 %. Statistical testing for the following hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected. This is the post-hoc analysis for the subgroup 'Baseline mTSS > 6'.

Comparison groups	Placebo (Randomized Set) v CZP 200 mg Q2W and CZP 400 mg Q4W (Randomized Set)
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.048 [10]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[10] - Difference of CZP 200 mg + 400 mg versus Placebo (and corresponding 95 % Confidence Interval and p-value) were estimated using an ANCOVA model with treatment, region and prior TNF-antagonist exposure as factors and Baseline mTSS score as a covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from Baseline (Week 0) over the whole Double-Blind, Dose-Blind and Open-Label Period.

Adverse event reporting additional description:

PBO arm subjects shifted either at Wk 16 or 24 to CZP treatment. Thus, PBO arm had lower exposure compared to the CZP arms. The exposure imbalance across treatment arms could lead to misinterpretation & questionable conclusions comparing simple counts & percentages of AEs. Thus, AEs reported while the patient was on PBO-treatment are not included.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	All CZP 200 mg Q2W

Reporting group description:

This arm includes all subjects who were randomized to CZP 200 mg Q2W at Baseline and those subjects who escaped or were re-randomized from Placebo to CZP 200 mg Q2W.

Subjects received one injection of 200 mg CZP and one injection of Placebo every two weeks to maintain the study blind.

Reporting group title	All CZP 200 mg + 400 mg

Reporting group description:

This arm shows all patients treated with Certolizumab Pegol (CZP) at least once. Hence, this arm is a combination of arm All CZP 200 mg Q2W and arm All CZP 400 mg Q4W.

Reporting group title	All CZP 400 mg Q4W

Reporting group description:

This arm includes all subjects who were randomized to CZP 400 mg Q4W at Baseline and those subjects who escaped or were re-randomized from Placebo to CZP 400 mg Q4W.

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

Serious adverse events	All CZP 200 mg Q2W	All CZP 200 mg + 400 mg	All CZP 400 mg Q4W
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 198 (24.75%)	100 / 393 (25.45%)	51 / 195 (26.15%)
number of deaths (all causes)	3	6	3
number of deaths resulting from adverse events	0	2	2
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	1 / 198 (0.51%)	2 / 393 (0.51%)	1 / 195 (0.51%)

occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 198 (0.51%)	3 / 393 (0.76%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Gastrointestinal cancer metastatic			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Ovarian cancer			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			

Pregnancy of partner			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy on contraceptive			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pyrexia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute stress disorder			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic stress disorder			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital prolapse			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 198 (0.00%)	2 / 393 (0.51%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulvar dysplasia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)

occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial rupture			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 198 (0.00%)	2 / 393 (0.51%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Animal bite			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic complication			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery thrombosis			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 198 (0.51%)	2 / 393 (0.51%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 198 (1.01%)	2 / 393 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 198 (0.51%)	2 / 393 (0.51%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 198 (1.52%)	3 / 393 (0.76%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 198 (0.51%)	2 / 393 (0.51%)	1 / 195 (0.51%)

occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysgraphia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Formication			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paralysis			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia oral			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)

occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	0 / 198 (0.00%)	2 / 393 (0.51%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 198 (0.51%)	3 / 393 (0.76%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 198 (0.00%)	2 / 393 (0.51%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary dyskinesia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)

occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Cutaneous lupus erythematosus			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	3 / 198 (1.52%)	4 / 393 (1.02%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 4	1 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	2 / 198 (1.01%)	3 / 393 (0.76%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 198 (0.00%)	2 / 393 (0.51%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lupus-like syndrome			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 198 (0.51%)	4 / 393 (1.02%)	3 / 195 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			

subjects affected / exposed	5 / 198 (2.53%)	8 / 393 (2.04%)	3 / 195 (1.54%)
occurrences causally related to treatment / all	0 / 5	0 / 12	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 198 (1.01%)	2 / 393 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 198 (0.51%)	4 / 393 (1.02%)	3 / 195 (1.54%)
occurrences causally related to treatment / all	0 / 1	3 / 5	3 / 4
deaths causally related to treatment / all	0 / 0	2 / 2	2 / 2
Bronchitis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIV infection			
subjects affected / exposed	1 / 198 (0.51%)	2 / 393 (0.51%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Staphylococcal abscess			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)

occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	2 / 198 (1.01%)	2 / 393 (0.51%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyoderma streptococcal			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Latent tuberculosis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 198 (0.51%)	2 / 393 (0.51%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic tonsillitis			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 198 (0.51%)	3 / 393 (0.76%)	2 / 195 (1.03%)
occurrences causally related to treatment / all	1 / 1	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 198 (0.51%)	1 / 393 (0.25%)	0 / 195 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 198 (0.00%)	1 / 393 (0.25%)	1 / 195 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	All CZP 200 mg Q2W	All CZP 200 mg + 400 mg	All CZP 400 mg Q4W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	158 / 198 (79.80%)	311 / 393 (79.13%)	153 / 195 (78.46%)
Vascular disorders			
Hypertension			
subjects affected / exposed	30 / 198 (15.15%)	46 / 393 (11.70%)	16 / 195 (8.21%)
occurrences (all)	33	53	20
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	15 / 198 (7.58%)	24 / 393 (6.11%)	9 / 195 (4.62%)
occurrences (all)	21	31	10
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 198 (8.59%)	32 / 393 (8.14%)	15 / 195 (7.69%)
occurrences (all)	23	48	25
Blood creatine phosphokinase increased			
subjects affected / exposed	15 / 198 (7.58%)	28 / 393 (7.12%)	13 / 195 (6.67%)
occurrences (all)	28	53	25
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 198 (4.55%)	20 / 393 (5.09%)	11 / 195 (5.64%)
occurrences (all)	13	30	17
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 198 (4.04%)	20 / 393 (5.09%)	12 / 195 (6.15%)
occurrences (all)	11	26	15
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 198 (4.04%)	22 / 393 (5.60%)	14 / 195 (7.18%)
occurrences (all)	9	23	14
Oropharyngeal pain			

subjects affected / exposed	6 / 198 (3.03%)	16 / 393 (4.07%)	10 / 195 (5.13%)
occurrences (all)	6	19	13
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 198 (9.09%)	35 / 393 (8.91%)	17 / 195 (8.72%)
occurrences (all)	19	39	20
Dizziness			
subjects affected / exposed	5 / 198 (2.53%)	15 / 393 (3.82%)	10 / 195 (5.13%)
occurrences (all)	5	15	10
Psychiatric disorders			
Depression			
subjects affected / exposed	11 / 198 (5.56%)	20 / 393 (5.09%)	9 / 195 (4.62%)
occurrences (all)	12	24	12
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 198 (7.58%)	26 / 393 (6.62%)	11 / 195 (5.64%)
occurrences (all)	20	35	15
Abdominal pain			
subjects affected / exposed	12 / 198 (6.06%)	21 / 393 (5.34%)	9 / 195 (4.62%)
occurrences (all)	13	23	10
Abdominal pain upper			
subjects affected / exposed	14 / 198 (7.07%)	19 / 393 (4.83%)	5 / 195 (2.56%)
occurrences (all)	16	25	9
Nausea			
subjects affected / exposed	10 / 198 (5.05%)	18 / 393 (4.58%)	8 / 195 (4.10%)
occurrences (all)	11	20	9
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	22 / 198 (11.11%)	41 / 393 (10.43%)	19 / 195 (9.74%)
occurrences (all)	31	52	21
Rash			
subjects affected / exposed	10 / 198 (5.05%)	19 / 393 (4.83%)	9 / 195 (4.62%)
occurrences (all)	16	25	9
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	24 / 198 (12.12%)	46 / 393 (11.70%)	22 / 195 (11.28%)
occurrences (all)	28	54	26

Psoriatic arthropathy			
subjects affected / exposed	24 / 198 (12.12%)	39 / 393 (9.92%)	15 / 195 (7.69%)
occurrences (all)	41	64	23
Arthralgia			
subjects affected / exposed	20 / 198 (10.10%)	38 / 393 (9.67%)	18 / 195 (9.23%)
occurrences (all)	28	56	28
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	44 / 198 (22.22%)	93 / 393 (23.66%)	49 / 195 (25.13%)
occurrences (all)	81	154	73
Nasopharyngitis			
subjects affected / exposed	45 / 198 (22.73%)	87 / 393 (22.14%)	42 / 195 (21.54%)
occurrences (all)	87	178	91
Pharyngitis			
subjects affected / exposed	24 / 198 (12.12%)	51 / 393 (12.98%)	27 / 195 (13.85%)
occurrences (all)	44	81	37
Bronchitis			
subjects affected / exposed	28 / 198 (14.14%)	50 / 393 (12.72%)	22 / 195 (11.28%)
occurrences (all)	36	65	29
Urinary tract infection			
subjects affected / exposed	13 / 198 (6.57%)	39 / 393 (9.92%)	26 / 195 (13.33%)
occurrences (all)	18	53	35
Sinusitis			
subjects affected / exposed	19 / 198 (9.60%)	32 / 393 (8.14%)	13 / 195 (6.67%)
occurrences (all)	32	65	33
Gastroenteritis			
subjects affected / exposed	14 / 198 (7.07%)	22 / 393 (5.60%)	8 / 195 (4.10%)
occurrences (all)	18	26	8
Oral herpes			
subjects affected / exposed	10 / 198 (5.05%)	21 / 393 (5.34%)	11 / 195 (5.64%)
occurrences (all)	25	43	18
Influenza			
subjects affected / exposed	13 / 198 (6.57%)	21 / 393 (5.34%)	8 / 195 (4.10%)
occurrences (all)	15	24	9
Tonsillitis			
subjects affected / exposed	11 / 198 (5.56%)	19 / 393 (4.83%)	8 / 195 (4.10%)

occurrences (all)	11	23	12
Rhinitis			
subjects affected / exposed	10 / 198 (5.05%)	19 / 393 (4.83%)	9 / 195 (4.62%)
occurrences (all)	11	20	9
Latent tuberculosis			
subjects affected / exposed	6 / 198 (3.03%)	18 / 393 (4.58%)	12 / 195 (6.15%)
occurrences (all)	6	18	12
Viral infection			
subjects affected / exposed	9 / 198 (4.55%)	16 / 393 (4.07%)	7 / 195 (3.59%)
occurrences (all)	12	19	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2009	The protocol was amended to adapt to the most recent scientific developments in the field. In addition, the Sponsor Study Physician information was updated, a few typographical errors were corrected, and some clarifications were made to the protocol text. The original final PsA001 protocol (25 Sep 2009) was approved internally by the Sponsor; however, Protocol Amendment 1 (23 Nov 2009) was the first version of the protocol to be submitted to any regulatory health authority. The following changes were made throughout the protocol: - The Sponsor Study Physician information was updated - The Classification Criteria for Psoriatic Arthritis (CASPAR) were added to the inclusion criteria - Leflunomide was added to the list of allowed DMARDs, and hydroxychloroquine (HCQ) and DMARD combinations were now prohibited - The effect of CZP on axial involvement in a subgroup of affected subjects (BASDAI ≥4) at Baseline was added as another secondary objective - Measurement of human leukocyte antigen B27 (HLA-B27) at Baseline was included - Permission was given for samples collected for measurement of CZP plasma concentration to be possibly used for exploratory biomarker (Dickkopf-related protein 1 [DKK1] and sclerostin) research - The swollen joint count and tender joint count assessments were changed from the 76/78 joints to the 66/68 joints evaluation - Clarification that assessment of arthritis should include consideration of both joint and skin components in both the Patient's and Physician's Global Assessments of Disease Activity (PtGADA and PhGADA, respectively) was added - Clarification that the PhGADA (Likert Scale) was to be used only for the Psoriatic Arthritis Response Criteria (PsARC) assessment was added - Clarification that PsA history included relevant family history and prior and concomitant medication history was added

21 April 2010	The following changes were made throughout the protocol: - FAS was replaced by the RS for the primary efficacy analyses. - The SAP was adjusted for multiple endpoints. A hierarchical test procedure was applied to protect the overall significance level of the multiplicity of dose groups and endpoints with a predefined order of hypotheses testing. - Assessment of subjects with a PhGAP rating of "clear" or "almost clear" was added as a secondary endpoint to evaluate psoriatic skin lesions. - The specification that vital signs were to be performed within 15 minutes prior to dosing was removed. - A definition of PASI assessments was added. Clarification was added that the dactylitis assessment was to be performed using the LDI basic according to Healy and Helliwell (2007) and Helliwell et al (2005). - Clarification was added that the enthesitis assessment was to be performed on the elbows, knees, and heels. - Description of the mNAPSI assessment was modified in accordance with Cassell et al, 2007. - Clarification was added that abatacept (ABA) was both a prohibited medication (if used within 3 months prior to BL) and a prohibited concomitant and and rescue treatment. - For tuberculosis (TB) testing, inconsistencies in visit referencing (eg, BL) with regards to purified protein derivative (PPD) tests were corrected to reference the Screening Visit. - Clarification that the cited liver function tests >2x ULN, creatinine>ULN, or white blood cells (WBCs) <3.0x109/L represent examples of clinically significant laboratory abnormalities, which would exclude subject entry into the study, was added to the appropriate exclusion criterion. - Clarification was added that 1 rescreening of subjects with latent TB who were unable to complete a minimum of 4 weeks of TB therapy within the Screening Period was permitted. - Clarification was added that if the Elispot was neg. at Screening, it would be repeated at W48 and W96 for subjects with a previously negative Elispot test result
22 November 2010	The protocol was amended to increase the approximate number of centers participating in this study and the approximate number of subjects who would be screened because of a higher than expected screen failure rate. In addition, Sponsor personnel and the corresponding contact information were updated. Administrative changes for internal consistency were also implemented. The following changes were made throughout the protocol: - The approximate number of subjects who were to be screened was increased from 500 to 700 - The approximate number of centers participating in the study was increased from 100 to 130 - Based on previous feedback from the FDA, all randomized subjects must be used for primary analysis; therefore, the statement that 375 subjects would be available for the primary efficacy analyses was deleted
30 January 2012	The protocol was amended to comply with new FDA Safety Reporting Requirements (Food and Drug Administration, Guidance for Industry, 2010) and the corresponding change to the UCB Protocol Template, language was added to the Assessment of Safety Section to clarify procedures for reporting relatedness of an serious adverse event (SAE) and to define anticipated SAEs. In addition, the name of the Sponsor, Sponsor personnel, and the corresponding contact information were updated. Administrative changes for internal consistency were also implemented. The following changes were made throughout the protocol: - For the assessment of socioprofessional status, housing status of the subject was not obtained by site personnel - Additional guidance to Investigators was provided for including the casual relationship of study medication between an SAE and study medication when completing the SAE report form - Anticipated SAEs were identified

25 January 2013	The protocol was amended to implement the extension of the Open-Label Treatment Period for an additional 58 weeks. The following changes were made throughout the protocol: - A new Clinical Project Manager was identified. - Wording regarding the extension of the Open-Label Treatment Period, additional BSA assessments, and new TB standards were added. - The list of biomarkers that may have been analyzed was updated. - Visit scheduling of Week 158 (Completion/Withdrawal Visit) was shifted to Week 216 and the last dosing visit of Week 156 was changed to occur at Week 214 for the 200mg Q2W regimen and Week 212 for the 400mg Q4W regimen. The regular last site visit and the final evaluation visit were combined to reduce the amount of investigations and visits. - Chest x-ray was requested additionally at Week 156 and at the Completion Visit Week 216/ Withdrawal. - Hand and foot x-rays were added at Week 168 and at Withdrawal Visit if hand and foot x-ray was performed more than 8 weeks prior to Withdrawal Visit. - Assessment of BSA und PASI for all subjects at Weeks 156, 168, 180, 192, 204, and 216/ Withdrawal. - PPD and interferon-gamma release assay (IGRA) tests were requested additionally at Weeks 48, 96, 156, and Week 216/ Withdrawal. - Definition of minimal disease activity was added. - The adverse event (AE) of interest section was updated to be consistent with current reporting requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported