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

Summary

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

Results information

Result version number	v2 (current)
This version publication date	01 February 2017
First version publication date	02 September 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	AS001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01087762
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy:

Background therapy was permitted as defined in the study protocol.

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	317
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is a multicenter study with 128 sites in North America, Latin America, Western Europe, and Central/Eastern Europe.
325 subjects are included in Randomized Set (RS) shown in Participant Flow for the interim period, and 315 for the final analysis (10 subjects dropped out before receiving a CZP dose), which is an Intention-to-Treat (ITT) dataset

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

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

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

Placebo : Matching Placebo to CZP injection.

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

Dosage and administration details:

Placebo administered sc.

Arm title	CZP 200 mg Q2W

Arm description:

Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.
At every visit, subjects received one injection of 200 mg CZP and one injection of Placebo to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

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

Arm type	Experimental

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

Dosage and administration details:

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

Arm title	CZP 400 mg Q4W

Arm description:

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

Placebo : Matching Placebo to CZP injection.

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

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

Dosage and administration details:

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

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

Period 2

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

Blinding implementation details:

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

Arms

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

Arm description:

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

Placebo : Matching Placebo to CZP injection.

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

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

Dosage and administration details:

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

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

Dosage and administration details:

Placebo administered sc.

Arm title	All CZP 400 mg

Arm description:

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

Placebo : Matching Placebo to CZP injection.

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

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

Dosage and administration details:

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

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

Dosage and administration details:

Placebo administered sc.

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

Baseline characteristics

Reporting groups[1]	
Reporting group title	Placebo

Reporting group description:

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

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

Placebo : Matching Placebo to CZP injection.

Reporting group title	CZP 200 mg Q2W

Reporting group description:

Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.
At every visit, subjects received one injection of 200 mg CZP and one injection of Placebo to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

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

Reporting group title	CZP 400 mg Q4W

Reporting group description:

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

Placebo : Matching Placebo to CZP injection.

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

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Only patients who received at least one dose of CZP were included in the final analysis.

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

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

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

End points reporting groups

Reporting group title	Placebo

Reporting group description:

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

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

Placebo : Matching Placebo to CZP injection.

Reporting group title	CZP 200 mg Q2W

Reporting group description:

Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.
At every visit, subjects received one injection of 200 mg CZP and one injection of Placebo to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

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

Reporting group title	CZP 400 mg Q4W

Reporting group description:

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

Placebo : Matching Placebo to CZP injection.

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

Reporting group title	All CZP 200 mg

Reporting group description:

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

Placebo : Matching Placebo to CZP injection.

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

Reporting group title	All CZP 400 mg

Reporting group description:

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

Placebo : Matching Placebo to CZP injection.

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

Subject analysis set title	Placebo (FAS)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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

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

Placebo : Matching Placebo to CZP injection.

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

Subject analysis set description:

Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W) from Week 6 onwards.
At every visit, subjects received one injection of 200 mg CZP and one injection of Placebo to maintain the study blind.

Placebo : Matching Placebo to CZP injection.

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

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

Subject analysis set description:

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

Placebo : Matching Placebo to CZP injection.

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

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

Subject analysis set description:

This arm shows a combination of arm CZP 200 mg Q2W and arm CZP 400 mg Q4W. Subjects received Certolizumab Pegol (CZP) 400 mg subcutaneous (sc) on Weeks 0, 2 and 4, followed by 200 mg CZP sc every 2 weeks (Q2W)/ 400 mg CZP sc every 4 weeks (Q4W) from Week 6/ Week 8 onwards.
Subjects in both CZP arms received additional placebo injections to maintain the study blind.
Placebo : Matching Placebo to CZP injection.

CZP 200 mg Q2W : 200 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 2 weeks (Q2W).
CZP 400 mg Q4W : 400 mg subcutaneous (sc) injection of Certolizumab Pegol (CZP) every 4 weeks (Q4W).

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

Subject analysis set description:

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

Placebo : Matching Placebo to CZP injection.

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

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

Subject analysis set description:

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

Placebo : Matching Placebo to CZP injection.

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

(Q4W).

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

Subject analysis set description:

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

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

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

End point description:

The ASAS20 is defined as an improvement of at least 20 % and absolute improvement of at least 1 unit on a 0 to 10 Numeric Rating Scale (NRS) in at least 3 of the 4 following domains:
- Patient's Global Assessment of Disease Activity
- Pain assessment (total spinal pain)
- Function (represented by Bath Ankylosing Spondylitis Functional Index (BASFI))
- Inflammation (the mean of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questions 5 and 6 concerning morning stiffness intensity and duration)

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

End point type	Primary

End point timeframe:

Week 12

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

Statistical analyses

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

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

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

Notes:

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

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

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

Notes:

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

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

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

End point description:

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

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

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

End point type	Secondary

End point timeframe:

Week 24

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

Statistical analyses

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W (FAS)
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Wald-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	37.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.4
upper limit	50

Notes:

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

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

Comparison groups	Placebo (FAS) v CZP 400 mg Q4W (FAS)

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 12

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

Statistical analyses

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 24

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

Statistical analyses

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 12

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

Statistical analyses

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

Comparison groups	Placebo (FAS) v CZP 200 mg Q2W and CZP 400 mg Q4W (FAS)
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	-1.12
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

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

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

End point title	Change from Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 24

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 24

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

Statistical analyses

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 12

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

Statistical analyses

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

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

Notes:

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

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

From Baseline to Week 24

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

Statistical analyses

Statistical analysis title	Difference in efficacy

Statistical analysis description:

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

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

Notes:

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

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to Week 12

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The SPARCC scoring method for lesions found on the Magnetic Resonance Imaging (MRI) is based on an abnormal increased signal on the Short-Tau-Inversion Recovery (STIR) sequence, representing bone marrow edema. Total Sacroiliac (SI) joint SPARCC score can range from 0 to 72 with higher scores indicating higher joint inflammation. A negative value in SPARCC change from Baseline indicates an improvement from Baseline. The higher the negative value the higher the reduction of inflammation.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

As per study design, placebo arm subjects shifted either at Week 16 or 24 to CZP treatment. For the Placebo (PBO) group, CZP data from PBO subjects are not utilized. The All CZP 200 mg + 400 mg group shows CZP 200 mg, CZP 400 mg and the escaped PBO subjects with their CZP data.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	All CZP 200 mg (Safety Analysis)

Reporting group description:

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

Placebo : Matching Placebo to CZP injection.

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

Reporting group title	All CZP 400 mg (Safety Analysis)

Reporting group description:

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

Placebo : Matching Placebo to CZP injection.

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

Reporting group title	All CZP 200 mg + 400 mg

Reporting group description:

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

Reporting group title	Placebo

Reporting group description:

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

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

Placebo : Matching Placebo to CZP injection.

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

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesterol granuloma			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Astrocytoma			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Morton's neuroma			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bone graft			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion induced			

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

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

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

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

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

subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory bowel disease			
subjects affected / exposed	0 / 158 (0.00%)	0 / 157 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 158 (0.00%)	2 / 157 (1.27%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis migration			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			

subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermal cyst			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureteric obstruction			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	0 / 158 (0.00%)	0 / 157 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	1 / 158 (0.63%)	1 / 157 (0.64%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	3 / 158 (1.90%)	0 / 157 (0.00%)	3 / 315 (0.95%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankylosing spondylitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycobacterial infection			
subjects affected / exposed	1 / 158 (0.63%)	1 / 157 (0.64%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal candidiasis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus infection			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster disseminated			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	1 / 158 (0.63%)	0 / 157 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 158 (1.90%)	0 / 157 (0.00%)	3 / 315 (0.95%)
occurrences causally related to treatment / all	1 / 5	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected dermal cyst			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 158 (0.00%)	1 / 157 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Latent tuberculosis			

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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 107 (4.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesterol granuloma			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of the			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Astrocytoma			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Morton's neuroma			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Bone graft			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abortion induced			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy on contraceptive			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			

subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diffuse alveolar damage			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal congestion			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal polyps			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Conversion disorder			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			

Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Joint dislocation				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meniscus lesion				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery disease				

subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Intracranial aneurysm			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Hilar lymphadenopathy			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			

subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paratracheal lymphadenopathy				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Retinal vein occlusion				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis ulcerative				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sigmoiditis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				

subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Crohn's disease				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inflammatory bowel disease				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholelithiasis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis migration				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				

Psoriasis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dermal cyst			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Ureteric obstruction			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Calculus ureteric			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Osteoarthritis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ankylosing spondylitis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spondylitis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal abscess				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mycobacterial infection				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal candidiasis				

subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster disseminated				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia legionella				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected dermal cyst				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Latent tuberculosis				
subjects affected / exposed	0 / 107 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				

subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute sinusitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All CZP 200 mg (Safety Analysis)	All CZP 400 mg (Safety Analysis)	All CZP 200 mg + 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 158 (89.87%)	127 / 157 (80.89%)	269 / 315 (85.40%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	14 / 158 (8.86%)	17 / 157 (10.83%)	31 / 315 (9.84%)
occurrences (all)	16	23	39

Alanine aminotransferase increased			
subjects affected / exposed	11 / 158 (6.96%)	8 / 157 (5.10%)	19 / 315 (6.03%)
occurrences (all)	14	10	24
Tuberculin test positive			
subjects affected / exposed	8 / 158 (5.06%)	7 / 157 (4.46%)	15 / 315 (4.76%)
occurrences (all)	8	7	15
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 158 (3.80%)	8 / 157 (5.10%)	14 / 315 (4.44%)
occurrences (all)	6	9	15
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	10 / 158 (6.33%)	9 / 157 (5.73%)	19 / 315 (6.03%)
occurrences (all)	18	11	29
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 158 (12.66%)	11 / 157 (7.01%)	31 / 315 (9.84%)
occurrences (all)	26	11	37
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 158 (10.76%)	18 / 157 (11.46%)	35 / 315 (11.11%)
occurrences (all)	25	31	56
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	7 / 158 (4.43%)	8 / 157 (5.10%)	15 / 315 (4.76%)
occurrences (all)	8	11	19
Eye disorders			
Uveitis			
subjects affected / exposed	11 / 158 (6.96%)	8 / 157 (5.10%)	19 / 315 (6.03%)
occurrences (all)	15	12	27
Conjunctivitis			
subjects affected / exposed	5 / 158 (3.16%)	8 / 157 (5.10%)	13 / 315 (4.13%)
occurrences (all)	6	9	15
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 158 (6.33%)	20 / 157 (12.74%)	30 / 315 (9.52%)
occurrences (all)	13	26	39
Gastritis			

subjects affected / exposed	8 / 158 (5.06%)	5 / 157 (3.18%)	13 / 315 (4.13%)
occurrences (all)	8	5	13
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 158 (8.23%)	11 / 157 (7.01%)	24 / 315 (7.62%)
occurrences (all)	16	13	29
Oropharyngeal pain			
subjects affected / exposed	12 / 158 (7.59%)	6 / 157 (3.82%)	18 / 315 (5.71%)
occurrences (all)	15	6	21
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	11 / 158 (6.96%)	14 / 157 (8.92%)	25 / 315 (7.94%)
occurrences (all)	15	18	33
Psoriasis			
subjects affected / exposed	8 / 158 (5.06%)	6 / 157 (3.82%)	14 / 315 (4.44%)
occurrences (all)	14	9	23
Eczema			
subjects affected / exposed	4 / 158 (2.53%)	8 / 157 (5.10%)	12 / 315 (3.81%)
occurrences (all)	6	13	19
Psychiatric disorders			
Depression			
subjects affected / exposed	9 / 158 (5.70%)	4 / 157 (2.55%)	13 / 315 (4.13%)
occurrences (all)	10	5	15
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 158 (13.92%)	11 / 157 (7.01%)	33 / 315 (10.48%)
occurrences (all)	42	20	62
Back pain			
subjects affected / exposed	14 / 158 (8.86%)	11 / 157 (7.01%)	25 / 315 (7.94%)
occurrences (all)	18	19	37
Spondylitis			
subjects affected / exposed	12 / 158 (7.59%)	13 / 157 (8.28%)	25 / 315 (7.94%)
occurrences (all)	22	14	36
Ankylosing spondylitis			
subjects affected / exposed	11 / 158 (6.96%)	5 / 157 (3.18%)	16 / 315 (5.08%)
occurrences (all)	17	8	25

Pain in extremity			
subjects affected / exposed	10 / 158 (6.33%)	3 / 157 (1.91%)	13 / 315 (4.13%)
occurrences (all)	11	4	15
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	47 / 158 (29.75%)	43 / 157 (27.39%)	90 / 315 (28.57%)
occurrences (all)	80	83	163
Upper respiratory tract infection			
subjects affected / exposed	35 / 158 (22.15%)	28 / 157 (17.83%)	63 / 315 (20.00%)
occurrences (all)	53	58	111
Bronchitis			
subjects affected / exposed	24 / 158 (15.19%)	17 / 157 (10.83%)	41 / 315 (13.02%)
occurrences (all)	28	18	46
Pharyngitis			
subjects affected / exposed	24 / 158 (15.19%)	11 / 157 (7.01%)	35 / 315 (11.11%)
occurrences (all)	36	17	53
Sinusitis			
subjects affected / exposed	17 / 158 (10.76%)	8 / 157 (5.10%)	25 / 315 (7.94%)
occurrences (all)	21	10	31
Urinary tract infection			
subjects affected / exposed	10 / 158 (6.33%)	11 / 157 (7.01%)	21 / 315 (6.67%)
occurrences (all)	17	15	32
Rhinitis			
subjects affected / exposed	15 / 158 (9.49%)	6 / 157 (3.82%)	21 / 315 (6.67%)
occurrences (all)	22	8	30
Influenza			
subjects affected / exposed	9 / 158 (5.70%)	11 / 157 (7.01%)	20 / 315 (6.35%)
occurrences (all)	10	14	24
Tonsillitis			
subjects affected / exposed	8 / 158 (5.06%)	9 / 157 (5.73%)	17 / 315 (5.40%)
occurrences (all)	10	11	21
Oral herpes			
subjects affected / exposed	9 / 158 (5.70%)	6 / 157 (3.82%)	15 / 315 (4.76%)
occurrences (all)	23	7	30
Cystitis			

subjects affected / exposed	8 / 158 (5.06%)	6 / 157 (3.82%)	14 / 315 (4.44%)
occurrences (all)	13	10	21
Gastroenteritis			
subjects affected / exposed	5 / 158 (3.16%)	9 / 157 (5.73%)	14 / 315 (4.44%)
occurrences (all)	5	9	14
Viral infection			
subjects affected / exposed	9 / 158 (5.70%)	4 / 157 (2.55%)	13 / 315 (4.13%)
occurrences (all)	10	4	14

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 107 (20.56%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Tuberculin test positive			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 107 (3.74%)		
occurrences (all)	4		
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 11		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	 0 / 107 (0.00%) 0		
Eye disorders Uveitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all)	 0 / 107 (0.00%) 0 0 / 107 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all)	 0 / 107 (0.00%) 0 0 / 107 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 0 / 107 (0.00%) 0 0 / 107 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Psoriasis subjects affected / exposed occurrences (all) Eczema	 2 / 107 (1.87%) 2 0 / 107 (0.00%) 0		

subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Spondylitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Ankylosing spondylitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences (all)	3		
Bronchitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Sinusitis			

subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	4 / 107 (3.74%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 107 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2009	The following changes were made throughout the protocol: - Inclusion criteria were broadened to include subjects meeting the ASAS clinical criteria and not limited only to subjects meeting the new ASAS imaging criteria. Subjects meeting the new imaging criteria represented at least 50% of subjects not meeting the mNY classification criteria. - Clarification was included that x-rays and MRIs documenting sacroiliitis for subjects meeting the new ASAS imaging criteria must be read by a radiologist (MRIs) and records (x-rays and MRIs) must be included in source documentation. - Update was made to permit samples collected for measurement of CZP plasma concentration to be possibly used for exploratory biomarker (Dickkopf-related protein 1 [DKK1] and sclerostin) research. - Update was made to Exclusion Criteria 6 and 7 to more clearly define exclusion of subjects with fibromyalgia. - The secondary objective assessment of subject symptomatic state was added, which included the secondary (Patient Acceptable Symptomatic State [PASS] and Physician Acceptable Symptomatic State) and exploratory (Patient's Global Impression of Change [PGIC]) variables. - Update was made to collect SI joint x-ray at Baseline for all subjects not receiving a Baseline MRI. - The schematic of the injection schedule was corrected to remove placebo injection from Week 48 in the CZP 200mg group. - Information on the possible use of other MRI reading criteria in addition to the Spondyloarthritis Research Consortium of Canada (SPARCC) criteria (such as Berlin or modified Berlin criteria) was included. - Clarification was added that the 44 joint counts include both swollen and tender joint counts. - Clarification was added that recording of axSpA history includes relevant family history and prior and concomitant medication history.

15 March 2010	The following changes were made throughout the protocol: - The Full Analysis Set (FAS) was replaced by the RS for primary efficacy analyses. - The SAP was adjusted for multiple endpoints including implementation of the following: Addition of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Weeks 12 and 24) and Bath Ankylosing Spondylitis Metrology Index (BASMI) (Weeks 12 and 24) to the key secondary variables. A hierarchical test procedure was applied to protect the overall significance level of the multiplicity of dose groups and endpoints with a predefined order of hypotheses testing for the following endpoints: ASAS20 response at Weeks 12 and 24 (200mg Q2W and 400mg Q4W), Bath Ankylosing Spondylitis Functional Index (BASFI) Weeks 12 and 24 (combined dose groups), BASDAI Weeks 12 and 24 (combined dose groups), and BASMI Weeks 12 and 24 (combined dose groups). - A marker for inflammation (C-reactive protein [CRP] >upper limit of normal [ULN]) was added to Inclusion Criterion #6. One retesting of subjects failing Screening due to CRP level was permitted. - Clarification was added that SI joint x-rays were performed at Baseline for all subjects. - Update was added that a SI joint x-ray performed <12 weeks (instead of <4 weeks) prior to the Baseline Visit may be used as the Baseline assessment provided that the film can be submitted and meets the requirements for central reading. - Clarification was added that subjects who were enrolled on the basis of meeting the imaging criteria must have been diagnosed on this basis prior to the Screening Visit. - Clarification was added that abatacept was both a prohibited medication (if used within 3 months prior to Baseline) and a prohibited concomitant and rescue treatment. - For TB testing, inconsistencies in visit referencing (eg, Baseline) with regards to purified protein derivative (PPD) tests were corrected to reference the Screening Visit. (Continued below)
15 March 2010	(Global Substantial Protocol Amendment #3 - 15-Mar-2010 - belongs to the Global Amendment #2) - Clarification that the cited liver function tests (LFTs) >2xULN, creatinine >ULN, or white blood cells (WBCs) <3.0x109/L represent examples of clinically significant laboratory abnormalities which would exclude subject entry into the study was added to Exclusion Criterion #29. - The statement requiring x-ray or MRI documenting sacroiliitis within 6 months of Screening was removed. - Clarification was added that rescreening of subjects with latent TB who were unable to complete a minimum of 4 weeks of TB therapy within the Screening Period was permitted. - Clarification was added that in addition to the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS), x-rays could be evaluated using other assessments. - Clarification was added that subjects meeting the definite AS diagnosis according to the mNY classification criteria were defined as subjects meeting the NY classification criteria in the context of this protocol. - Clarification on the definition for inflammatory back pain for axSpA was added.

06 December 2010	The following changes were made throughout the protocol: - The approximate number of subjects to be screened was increased from 400 to 600. - The approximate number of sites participating in the study was increased from 100 to 130. - Inclusion Criterion #5 was clarified to ensure that the symptom duration of adult-onset axSpA was at least 3 months and to reduce confusion about the requirements of the study population. - Inclusion Criterion #6 (and the respective study population information) was expanded to include subjects with MRI evidence of sacroiliitis. - Select sites could conduct prescreening activities, and prior to these activities, subjects were to read and sign a separate informed consent form that had been approved by an IEC/IRB and the Sponsor and which complied with regulatory requirements. - The specification for vital signs to be collected within 15 minutes prior to dosing was removed. - In several locations in the protocol, it was clarified that pregnancy testing should be done on women of childbearing potential. - It was clarified that the TB test would be repeated at Week 48 and Week 96 for subjects with a previously negative test result. - As the batch number was not included on the label, this information was removed from the labeling section of the protocol. - It was clarified that Investigators and subjects would remain blind to the assigned CZP dose regimen until the subject reaches the Week 48 Visit. - The sample size for each treatment group required to detect statistically significant differences in ASAS20 was changed from 100 to 105 because of a previous FDA request that the primary analysis population be changed from FAS to all randomized subjects. - Sponsor personnel and the corresponding contact information were updated. - Various administrative adjustments for internal consistency were made.
27 April 2011	The following global changes were made throughout the protocol: - The company name was changed from SCHWARZ BIOSCIENCES, GmbH, A Member of the UCB Group of Companies, to UCB BIOSCIENCES GmbH. - Addition of the requirement for MRI at Week 48. - The addition of a second interim analysis after all subjects complete Week 48.

18 January 2013	Protocol Amendment 5 (18 Jan 2013) was implemented to extend the open-label period for an additional 48 weeks. In order to obtain more information about the long-term impact of the use of CZP on structural damage spine x-ray, SI joint x-ray and MRI should have been repeated at the Completion Visit (or Early Withdrawal Visit). Within this amendment, new UCB internal standards for procedures regarding TB detection and monitoring were implemented in order to comply with the revised UCB policy applied to all UCBsponsored studies that included subjects with immunological diseases, who were at increased risk of TB infection either associated with the investigational drug, underlying disease, concomitant treatments, or other medical or sociological factors. These instructions are evidence-based and reflect the updated recommendations of various national guidelines Centers for Disease Control and Prevention diagnosis of latent TB infection. With respect to new scientific evidence, the list of biomarkers that may be of interest for later analysis was updated and alternative methods of analysis of CZP and its constituent moieties were added. The following global changes were made throughout the protocol: - New Clinical Project Manager, Biostatistician, and Clinical Program Director. - Wording regarding the extension of the open-label period. - Wording regarding the additional Investigations. - Wording regarding the new TB standards. - List of biomarkers that may be of interest for analysis was updated. - Visit scheduling of Week 158 (Completion/Early Withdrawal Visit) was shifted to Week 204 and last dosing visit at Week 156 now occurred at Week 202 for the Q2W regimen and Week 200 for the Q4W regimen. Regular last on-site visit and the final evaluation visit were combined to reduce the amount of investigations. - Chest x-ray was requested additionally at Week 156 and at Completion Visit (Week 204)/Early Withdrawal. (Continued below)

18 January 2013	(Global Substantial Protocol Amendment #7 - 18-Jan-2013 - belongs to the Global Amendment #6) - Spine x-ray, SI joint x-ray and MRI of spine and SI-joint were requested at the Completion Visit Week 204/Early Withdrawal. - Injections should have been administered having a minimum of 10 days between CZP 200mg Q2W injections and a minimum of 20 days between CZP 400mg Q4W injections. - Injections missed due to a reasonable interfering adverse event (AE), that did not allow administration of an anti-TNF due to safety reasons, were not to have been considered for the evaluation of subject compliance. - An error in the description of the ASAS definition was corrected in Section 9.1.1 (of the protocol). Interim analyses of database lock 1 and 2 were performed with the hereby corrected parameters according to the international standards. The modified definition as described within Protocol Amendment 4 was evaluated additionally in the interim analysis of database lock 1 only. - An error in the description of the BASMI evaluation in Section 9.1.8 (of the protocol) was corrected. Now the description matches the naming of the “linear BASMI” according to secondary efficacy variables described in Section 4.1.2 (of the protocol). - The AE of interest Section 11.3 (of the protocol) was updated to be consistent with current reporting requirements.
15 March 2013	Protocol Amendment 6 implemented administrative changes to correct errors that existed in Protocol Amendment 5.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported