Clinical trial results:
A Randomized, Double-Blind, Parallel-Group, Placebo- and Active-Controlled, Multicenter Phase III Study of the Efficacy and Safety of Olokizumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Inadequately Controlled by Methotrexate Therapy

Summary

EudraCT number	2015-005307-83
Trial protocol	LV CZ DE LT HU PL BG RO
Global end of trial date	05 November 2019

Results information

Result version number	v1 (current)
This version publication date	15 November 2020
First version publication date	15 November 2020

Trial information

Trial identification

Sponsor protocol code	CL04041023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02760407
WHO universal trial number (UTN)	-
Other trial identifiers	IND No: 104933

Notes:

Sponsors

Sponsor organisation name	R-Pharm International
Sponsor organisation address	19 1, Berzarina Street, Moscow, Russian Federation, 123154
Public contact	Medical Department, R-Pharm International, +7 495 956 7937,
Scientific contact	Medical Department, R-Pharm International, +7 495 956 7937,

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	05 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of Olokizumab (OKZ) 64 milligrams (mg) administered subcutaneously (SC) once every 2 weeks (q2w) or once every 4 weeks (q4w) plus methotrexate (MTX) relative to placebo plus MTX and non-inferiority of OKZ 64 mg q2w or q4w administered SC plus MTX relative to Adalimumab plus MTX with respect to the American College of Rheumatology 20% response criteria (ACR20) at Week 12 in subjects with moderately to severely active rheumatoid arthritis (RA) inadequately controlled by MTX therapy.

Protection of trial subjects:

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation, Good Clinical Practice Guidelines, and applicable laws and regulations.

Background therapy:

Stable MTX dose was continued during the study. Folic acid ≥5 mg per week or equivalent was required during the study.

Evidence for comparator: -

Actual start date of recruitment	06 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 308
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Bulgaria: 65
Country: Number of subjects enrolled	Czech Republic: 189
Country: Number of subjects enrolled	Estonia: 13
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Hungary: 51
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Lithuania: 74
Country: Number of subjects enrolled	Argentina: 153
Country: Number of subjects enrolled	Brazil: 112
Country: Number of subjects enrolled	Colombia: 59
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Mexico: 215

Country: Number of subjects enrolled	Russian Federation: 77
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United States: 257
Worldwide total number of subjects	1648
EEA total number of subjects	756

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)	1327
From 65 to 84 years	320
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter Phase III study conducted at 209 study centers in 18 countries between 06 June 2016 and 05 November 2019. A total of 3359 subjects were screened, of which 1711 subjects were screen failures and 1648 subjects were randomized in the study.

Pre-assignment

Screening details:

Subjects with moderately to severely active, adult onset, RA with an inadequate response to MTX therapy for at least 12 weeks prior to Screening were assessed for eligibility. Eligible subjects were randomized in a 2:2:2:1 ratio to receive 64 mg OKZ q4w, 64 mg OKZ q2w, adalimumab 40 mg q2w, or placebo in a 24-week double-blind treatment period.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Since the study treatments were distinguishable, they were prepared by the unblinded pharmacist (or their unblinded designee) and administered by a trained, unblinded study team member who was not involved in the management of study subjects.

Arms

Are arms mutually exclusive?	Yes
Arm title	OKZ 64 mg q4w

Arm description:

Subjects received a SC injection of OKZ 64 mg q4w alternating with SC injections of placebo q4w to maintain blinding and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional open-label extension (OLE) study. Subjects who did not consent to participate in the OLE study attended the End of Treatment (EoT) Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Arm type	Experimental
Investigational medicinal product name	Olokizumab
Investigational medicinal product code	
Other name	OKZ, CDP6038, L04041
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 64 mg q4w OKZ by SC injection in either abdomen or thigh, prepared in blinded syringes of 0.4 milliliter (mL).

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

Dosage and administration details:

Subjects received placebo (sodium chloride 0.9%) q4w by SC injection in either abdomen or thigh, prepared in blinded syringes of 0.4 mL.

Arm title	OKZ 64 mg q2w

Arm description:

Subjects received a SC injection of OKZ 64 mg q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Arm type	Experimental
Investigational medicinal product name	Olokizumab
Investigational medicinal product code	
Other name	OKZ, CDP6038, L04041
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 64 mg q2w OKZ by SC injection in either abdomen or thigh, prepared in blinded syringes of 0.4 mL.

Arm title	Adalimumab 40 mg q2w

Arm description:

Subjects received a SC injection of adalimumab 40 mg q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	Humira®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 40 mg q2w adalimumab by SC injection in either abdomen or thigh, prepared in blinded syringes of either 0.4 or 0.8 mL.

Arm title	Placebo

Arm description:

Subjects received a SC injection of Placebo q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

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

Dosage and administration details:

Subjects received placebo (sodium chloride 0.9%) q2w by SC injection in either abdomen or thigh, prepared in blinded syringes of 0.4 mL.

Number of subjects in period 1	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w
Started	479	464	462
Received Treatment	478	462	462
Completed Treatment Period	437 [1]	421	413
Continued into Safety Follow Up Period	37 [2]	28 [3]	35 [4]
Enrolled in OLE	422 [5]	410 [6]	397 [7]
Completed	443	421	412
Not completed	36	43	50
Consent withdrawn by subject	25	31	37
Other	8	2	8
Death	2	3	1
Lost to follow-up	1	7	4

Number of subjects in period 1	Placebo
Started	243
Received Treatment	243
Completed Treatment Period	208
Continued into Safety Follow Up Period	17 [8]
Enrolled in OLE	199 [9]
Completed	207
Not completed	36
Consent withdrawn by subject	25
Other	4
Death	1
Lost to follow-up	6

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.
[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.
[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The subjects in each milestone is for information only and does not impact the number of subjects that completed the study.

Baseline characteristics

Reporting groups	
Reporting group title	OKZ 64 mg q4w
Reporting group description:	
Subjects received a SC injection of OKZ 64 mg q4w alternating with SC injections of placebo q4w to maintain blinding and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional open-label extension (OLE) study. Subjects who did not consent to participate in the OLE study attended the End of Treatment (EoT) Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.	
Reporting group title	OKZ 64 mg q2w
Reporting group description:	
Subjects received a SC injection of OKZ 64 mg q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.	
Reporting group title	Adalimumab 40 mg q2w
Reporting group description:	
Subjects received a SC injection of adalimumab 40 mg q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.	
Reporting group title	Placebo
Reporting group description:	
Subjects received a SC injection of Placebo q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.	

Reporting group values	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w
Number of subjects	479	464	462
Age categorical Units: Subjects			
Adults (18-64 years)	389	379	367
From 65-84 years	90	85	95
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.7	53.3	54.3
standard deviation	± 12.09	± 11.92	± 12.32
Gender categorical Units: Subjects			
Female	378	352	363
Male	101	112	99
Race Units: Subjects			
Asian	6	10	4
Black or African American	15	20	23

White	406	382	385
Other / Mixed	52	52	50

Reporting group values	Placebo	Total	
Number of subjects	243	1648	
Age categorical Units: Subjects			
Adults (18-64 years)	192	1327	
From 65-84 years	50	320	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	54.7		
standard deviation	± 11.85	-	
Gender categorical Units: Subjects			
Female	190	1283	
Male	53	365	
Race Units: Subjects			
Asian	5	25	
Black or African American	11	69	
White	203	1376	
Other / Mixed	24	178	

End points

End points reporting groups

Reporting group title	OKZ 64 mg q4w

Reporting group description:

Subjects received a SC injection of OKZ 64 mg q4w alternating with SC injections of placebo q4w to maintain blinding and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional open-label extension (OLE) study. Subjects who did not consent to participate in the OLE study attended the End of Treatment (EoT) Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Reporting group title	OKZ 64 mg q2w

Reporting group description:

Subjects received a SC injection of OKZ 64 mg q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Reporting group title	Adalimumab 40 mg q2w

Reporting group description:

Subjects received a SC injection of adalimumab 40 mg q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Reporting group title	Placebo

Reporting group description:

Subjects received a SC injection of Placebo q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Primary: Percentage of Subjects Meeting the ACR20 at Week 12 (OKZ Comparison with Placebo)

End point title	Percentage of Subjects Meeting the ACR20 at Week 12 (OKZ Comparison with Placebo)[1]

End point description:

To meet ACR20 response criteria at Week 12, a subject must have had at least 20% improvement from baseline in the following ACR Core Set values:
• Tender joint count (TJC) (68 joint count)
• Swollen joint count (SJC) (66 joint count)
An improvement of at least 20% from baseline in at least 3 of the following 5 components: 1) Subject Global Assessment of Disease Activity (Visual Analog Scale [VAS]); 2) Subject Assessment of Pain (VAS); 3) Health Assessment Questionnaire - Disability Index (HAQ-DI); 4) Physician Global Assessment (VAS); 5) Level of acute phase reactant (C-reactive protein [CRP]).

A responder was a subject meeting the ACR20 criteria and remaining on randomized treatment and in the study at Week 12. Analysis was performed on the intent-to-treat (ITT) population, which included all randomized subjects.

End point type	Primary

End point timeframe:

From Baseline to Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reporting group "Adalimumab 40 mg q2w" was not analyzed for this endpoint.

End point values	OKZ 64 mg q4w	OKZ 64 mg q2w	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	479	464	243	
Units: Percentage of subjects				
number (not applicable)	71.4	70.3	44.4	

Statistical analyses

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Placebo
Comparison groups	OKZ 64 mg q4w v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.27
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.183
upper limit	0.352

Notes:

[2] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Placebo
Comparison groups	OKZ 64 mg q2w v Placebo
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.258
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.171
upper limit	0.341

Notes:

[3] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Secondary: Percentage of Subjects Meeting the ACR20 at Week 12 (OKZ Comparison

with Adalimumab)	
End point title	Percentage of Subjects Meeting the ACR20 at Week 12 (OKZ Comparison with Adalimumab)

End point description:

To meet ACR20 response criteria at Week 12, a subject must have had at least 20% improvement from baseline in the following ACR Core Set values:
• TJC (68 joint count)
• SJC (66 joint count)
An improvement of at least 20% from baseline in at least 3 of the following 5 components: 1) Subject Global Assessment of Disease Activity (VAS); 2) Subject Assessment of Pain (VAS); 3) HAQ-DI; 4) Physician Global Assessment (VAS); 5) Level of acute phase reactant (CRP).

A responder was a subject meeting the ACR20 criteria and remaining on randomized treatment and in the study at Week 12. Analysis was performed on the ITT population, which included all randomized subjects.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	479	464	462	243
Units: Percentage of subjects				
number (not applicable)	71.4	70.3	66.9	44.4

Statistical analyses

Statistical analysis title	Comparison of Adalimumab 40 mg q2w Vs Placebo
Comparison groups	Adalimumab 40 mg q2w v Placebo
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.224
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.148
upper limit	0.298

Notes:

[4] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Adalimumab 40mg q2w
Comparison groups	Adalimumab 40 mg q2w v OKZ 64 mg q4w

Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Risk difference (RD)
Point estimate	0.045
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.022
upper limit	0.112

Notes:

[5] - Non-inferiority for each OKZ dosing regimen versus adalimumab is achieved if the lower limit of the 97.5% confidence interval is greater than the protocol defined non-inferiority margin of -12%.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q2w v Adalimumab 40 mg q2w
Number of subjects included in analysis	926
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Risk difference (RD)
Point estimate	0.034
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.035
upper limit	0.102

Notes:

[6] - Non-inferiority for each OKZ dosing regimen versus adalimumab is achieved if the lower limit of the 97.5% confidence interval is greater than the protocol defined non-inferiority margin of -12%.

Secondary: Percentage of Subjects Achieving Low Disease Activity, Defined as Disease Activity Score 28-Joint Count CRP (DAS 28 [CRP]) <3.2 at Week 12

End point title	Percentage of Subjects Achieving Low Disease Activity, Defined as Disease Activity Score 28-Joint Count CRP (DAS 28 [CRP]) <3.2 at Week 12

End point description:

The DAS28 (CRP) was calculated using the SJC (28 joints), TJC (28 joints), CRP level (mg/mL), and the Subject Global Assessment of Disease Activity (VAS) (in millimeters) according to the formula:
DAS28 (CRP) = $0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.36 \times \ln(CRP + 1) + 0.014 \times$ Subject Global Assessment of Disease Activity (VAS) + 0.96.
The 28 joints evaluated for the SJC and TJC were: shoulders, elbows, wrists, hands and knees. Subjects who remained on randomized treatment and who were in the study at Week 12 and had a DAS28 (CRP) <3.2 were classed as having low disease activity. Analysis was performed on the ITT population which included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 12

End point values	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	479	464	462	243
Units: Percentage of subjects				
number (not applicable)	45.7	45.3	38.3	12.8

Statistical analyses

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Placebo
Comparison groups	OKZ 64 mg q4w v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.33
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.255
upper limit	0.395

Notes:

[7] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Placebo
Comparison groups	OKZ 64 mg q2w v Placebo
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.325
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.25
upper limit	0.391

Notes:

[8] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of Adalimumab 40 mg q2w Vs Placebo
Comparison groups	Adalimumab 40 mg q2w v Placebo

Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.256
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.191
upper limit	0.313

Notes:

[9] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q4w v Adalimumab 40 mg q2w
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Risk difference (RD)
Point estimate	0.074
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.002
upper limit	0.145

Notes:

[10] - Non-inferiority for each OKZ dosing regimen versus adalimumab is achieved if the lower limit of the 97.5% confidence interval is greater than the protocol defined non-inferiority margin of -7.5%.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q2w v Adalimumab 40 mg q2w
Number of subjects included in analysis	926
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	Risk difference (RD)
Point estimate	0.069
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.003
upper limit	0.141

Notes:

[11] - Non-inferiority for each OKZ dosing regimen versus adalimumab is achieved if the lower limit of the 97.5% confidence interval is greater than the protocol defined non-inferiority margin of -7.5%.

Secondary: Mean Change from Baseline to Week 12 in HAQ-DI

End point title	Mean Change from Baseline to Week 12 in HAQ-DI

End point description:

The HAQ-DI is a patient reported questionnaire that provided an assessment of the impact of the disease and its treatment on physical function. The HAQ-DI assessed the degree of difficulty

experienced in 8 domains of daily living activities using 20 questions. For each question, the level of difficulty was scored from 0 to 3 where 0 = without any difficulty, 1 = with some difficulty, 2 = much difficulty, and 3 = unable to do. Each category was scored by taking the maximum score of each question. The HAQ-DI was calculated by dividing the sum of the category scores by the number of categories with at least 1 question answered. A decrease from baseline indicated an improvement in physical ability.

Analysis of covariance (ANCOVA) with treatment as fixed effect and baseline value as covariate was used to determine Least Square Mean (LSM) change from baseline for the ITT population, which included all randomized subjects.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	423	404	394	197
Units: Units on HAQ-DI scale				
least squares mean (standard error)	-0.61 (± 0.026)	-0.64 (± 0.027)	-0.61 (± 0.027)	-0.42 (± 0.038)

Statistical analyses

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Placebo
Comparison groups	OKZ 64 mg q4w v Placebo
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001 [13]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.19
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.29
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[12] - ANCOVA model included treatment as fixed effect and baseline value as a covariate. LSMs and P-value were obtained using Rubins's rule.
[13] - P-values represent a 1-sided combined test for treatment effect from the ANCOVA model.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Placebo
Comparison groups	OKZ 64 mg q2w v Placebo

Number of subjects included in analysis	601
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.0001 [15]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.22
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.33
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[14] - ANCOVA model included treatment as fixed effect and baseline value as a covariate. LSMs and P-value were obtained using Rubins's rule.
[15] - P-values represent a 1-sided combined test for treatment effect from the ANCOVA model.

Statistical analysis title	Comparison of Adalimumab 40 mg q2w Vs Placebo
Comparison groups	Adalimumab 40 mg q2w v Placebo
Number of subjects included in analysis	591
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	LSM difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[16] - ANCOVA model included treatment as fixed effect and baseline value as a covariate. LSMs were obtained using Rubins's rule.

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q4w v Adalimumab 40 mg q2w
Number of subjects included in analysis	817
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
Parameter estimate	LSM difference
Point estimate	0
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.08
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

[17] - ANCOVA model included treatment as fixed effect and baseline value as a covariate. LSMs were obtained using Rubins's rule.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q2w v Adalimumab 40 mg q2w
Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
Parameter estimate	LSM difference
Point estimate	-0.03
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.12
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

[18] - ANCOVA model included treatment as fixed effect and baseline value as a covariate. LSMs were obtained using Rubins's rule.

Secondary: Percentage of Subjects Achieving American College of Rheumatology 50% Response Criteria (ACR50) at Week 24

End point title	Percentage of Subjects Achieving American College of Rheumatology 50% Response Criteria (ACR50) at Week 24

End point description:

To meet ACR50 response criteria at Week 24, a subject must have had at least 50% improvement from baseline in the following ACR Core Set values:
• TJC (68 joint count)
• SJC (66 joint count)
An improvement of at least 50% in at least 3 of the following 5 components: 1) Subject Global Assessment of Disease Activity (VAS); 2) Subject Assessment of Pain (VAS); 3) HAQ-DI; 4) Physician Global Assessment (VAS); 5) Level of acute phase reactant (CRP).

Subjects must have been remaining on randomized treatment and in the study at Week 24. Analysis was performed on the ITT population, which included all randomized subjects.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	479	464	462	243
Units: Percentage of subjects				
number (not applicable)	50.1	50.4	46.3	22.6

Statistical analyses

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Placebo
Comparison groups	OKZ 64 mg q4w v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.275
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.192
upper limit	0.349

Notes:

[19] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Placebo
Comparison groups	OKZ 64 mg q2w v Placebo
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.278
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.195
upper limit	0.353

Notes:

[20] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of Adalimumab 40 mg q2w Vs Placebo
Comparison groups	Adalimumab 40 mg q2w v Placebo
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0.237
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.165
upper limit	0.303

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q4w v Adalimumab 40 mg q2w
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
Parameter estimate	Risk difference (RD)
Point estimate	0.038
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.035
upper limit	0.11

Notes:

[21] - Confidence Interval is calculated using Newcombe hybrid score method.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q2w v Adalimumab 40 mg q2w
Number of subjects included in analysis	926
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
Parameter estimate	Risk difference (RD)
Point estimate	0.041
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.032
upper limit	0.114

Notes:

[22] - Confidence Interval is calculated using Newcombe hybrid score method.

Secondary: Percentage of Subjects Achieving Remission, Defined as Clinical Disease Activity Index (CDAI) ≤2.8 (Remission) at Week 24

End point title	Percentage of Subjects Achieving Remission, Defined as Clinical Disease Activity Index (CDAI) ≤2.8 (Remission) at Week 24

End point description:

The CDAI was calculated using the SJC (28 joints), TJC (28 joints), the Subject Global Assessment of Disease Activity (VAS) (in centimeters), and the Physician Global Assessment (VAS) (in centimeters) according to the formula:
CDAI = SJC + TJC + Subject Global Assessment of Disease Activity (VAS) + Physician Global Assessment (VAS).

Subjects remaining on randomized treatment and in the study at Week 24 and with a CDAI of ≤2.8 were classed as in remission. Analysis was performed on the ITT population, which included all randomized subjects.

End point type	Secondary

End point timeframe:

At Week 24

End point values	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	479	464	462	243
Units: Percentage of subjects				
number (not applicable)	12.1	11.2	13.0	4.1

Statistical analyses

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Placebo
Comparison groups	OKZ 64 mg q4w v Placebo
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [23]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.08
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.031
upper limit	0.123

Notes:

[23] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Placebo
Comparison groups	OKZ 64 mg q2w v Placebo
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 [24]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.071
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.022
upper limit	0.113

Notes:

[24] - P-values are 1-sided α=0.025 significance level from 2x2 chi-square test.

Statistical analysis title	Comparison of Adalimumab 40 mg q2w Vs Placebo
Comparison groups	Adalimumab 40 mg q2w v Placebo

Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.127

Statistical analysis title	Comparison of OKZ 64 mg q4w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q4w v Adalimumab 40 mg q2w
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
Parameter estimate	Risk difference (RD)
Point estimate	-0.009
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.058
upper limit	0.04

Notes:

[25] - Confidence Interval is calculated using Newcombe hybrid score method.

Statistical analysis title	Comparison of OKZ 64 mg q2w Vs Adalimumab 40mg q2w
Comparison groups	OKZ 64 mg q2w v Adalimumab 40 mg q2w
Number of subjects included in analysis	926
Analysis specification	Pre-specified
Analysis type	non-inferiority[26]
Parameter estimate	Risk difference (RD)
Point estimate	-0.018
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.066
upper limit	0.031

Notes:

[26] - Confidence Interval is calculated using Newcombe hybrid score method.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) were recorded after the first dose of the study treatment until the last visit of the subject in the study (up to 44 weeks in total) regardless of relationship to study treatment.

Adverse event reporting additional description:

The safety population included all subjects who received at least 1 dose of study treatment.
Data for TEAEs were reported below. A TEAE was defined as an adverse event that first occurred or worsened in severity after the first dose of the study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	OKZ 64 mg q4w

Reporting group description:

Subjects received a SC injection of OKZ 64 mg q4w alternating with SC injections of placebo q4w to maintain blinding and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Reporting group title	OKZ 64 mg q2w

Reporting group description:

Subjects received a SC injection of OKZ 64 mg q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Reporting group title	Adalimumab 40 mg q2w

Reporting group description:

Subjects received a SC injection of adalimumab 40 mg q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Reporting group title	Placebo

Reporting group description:

Subjects received a SC injection of Placebo q2w and stable dose of MTX. The last dose of study treatment was at Week 22 of the Treatment Period from Week 0 to Week 24. After completion of the double-blind Treatment Period at Week 24, subjects were offered the opportunity to enter the optional OLE study. Subjects who did not consent to participate in the OLE study attended the EoT Visit at Week 24. After the EoT Visit, these subjects were scheduled for 3 Safety Follow-Up Visits up to Week 44.

Serious adverse events	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 477 (4.19%)	22 / 463 (4.75%)	26 / 462 (5.63%)
number of deaths (all causes)	2	3	1
number of deaths resulting from adverse events	2	3	1

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 477 (0.21%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	0 / 462 (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
Bladder transitional cell carcinoma stage IV			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial carcinoma			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma stage III			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	0 / 462 (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
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 477 (0.21%)	1 / 463 (0.22%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Surgery			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Injection site inflammation			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyp			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sudden death			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	0 / 462 (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
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	2 / 462 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid lung			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 477 (0.42%)	1 / 463 (0.22%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	2 / 2	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			

subjects affected / exposed	0 / 477 (0.00%)	2 / 463 (0.43%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	0 / 462 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	0 / 462 (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
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic anaemia			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Cataract			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic steatosis			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 477 (0.21%)	1 / 463 (0.22%)	6 / 462 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 1	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 477 (0.21%)	1 / 463 (0.22%)	2 / 462 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1

Urosepsis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	2 / 462 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 477 (0.42%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 477 (0.21%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	2 / 462 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	0 / 462 (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
Appendicitis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratouveitis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	0 / 462 (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
Latent tuberculosis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lyme disease			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			

subjects affected / exposed	1 / 477 (0.21%)	0 / 463 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 477 (0.00%)	1 / 463 (0.22%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 477 (0.00%)	0 / 463 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	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	12 / 243 (4.94%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 243 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			

subjects affected / exposed	1 / 243 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder transitional cell carcinoma stage IV				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchial carcinoma				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leiomyoma				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma stage III				
subjects affected / exposed	1 / 243 (0.41%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				

Surgery			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Injection site inflammation			
subjects affected / exposed	0 / 243 (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	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Polyp			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 243 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			

subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rheumatoid lung			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 243 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 243 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Tibia fracture				
subjects affected / exposed	1 / 243 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Pericarditis				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Ischaemic stroke			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Microcytic anaemia			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 243 (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 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum intestinal			

subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal inflammation			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumoperitoneum			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 243 (0.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic steatosis			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Intervertebral disc disorder				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint effusion				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	2 / 243 (0.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral discitis				

subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal abscess			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 243 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 243 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Keratouveitis			

subjects affected / exposed	1 / 243 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Latent tuberculosis				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lyme disease				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis streptococcal				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 243 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 243 (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 / 243 (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: 4 %

Non-serious adverse events	OKZ 64 mg q4w	OKZ 64 mg q2w	Adalimumab 40 mg q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	177 / 477 (37.11%)	183 / 463 (39.52%)	129 / 462 (27.92%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	53 / 477 (11.11%)	41 / 463 (8.86%)	9 / 462 (1.95%)
occurrences (all)	88	70	20
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 477 (5.03%)	23 / 463 (4.97%)	8 / 462 (1.73%)
occurrences (all)	38	27	15
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 477 (5.66%)	25 / 463 (5.40%)	13 / 462 (2.81%)
occurrences (all)	31	26	13
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 477 (2.31%)	10 / 463 (2.16%)	14 / 462 (3.03%)
occurrences (all)	12	11	17
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	8 / 477 (1.68%)	8 / 463 (1.73%)	20 / 462 (4.33%)
occurrences (all)	8	12	51
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 477 (5.45%)	29 / 463 (6.26%)	29 / 462 (6.28%)
occurrences (all)	34	35	32
Upper respiratory tract infection			
subjects affected / exposed	29 / 477 (6.08%)	28 / 463 (6.05%)	26 / 462 (5.63%)
occurrences (all)	33	31	30
Urinary tract infection			

subjects affected / exposed	14 / 477 (2.94%)	7 / 463 (1.51%)	19 / 462 (4.11%)
occurrences (all)	14	9	20
Bronchitis			
subjects affected / exposed	10 / 477 (2.10%)	12 / 463 (2.59%)	11 / 462 (2.38%)
occurrences (all)	10	12	13
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	20 / 477 (4.19%)	29 / 463 (6.26%)	6 / 462 (1.30%)
occurrences (all)	20	29	6
Dyslipidaemia			
subjects affected / exposed	15 / 477 (3.14%)	25 / 463 (5.40%)	4 / 462 (0.87%)
occurrences (all)	15	28	4
Hyperlipidaemia			
subjects affected / exposed	10 / 477 (2.10%)	22 / 463 (4.75%)	5 / 462 (1.08%)
occurrences (all)	10	24	6

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 243 (29.22%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 243 (1.65%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 243 (0.82%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 243 (3.29%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 243 (4.94%)		
occurrences (all)	12		
General disorders and administration site conditions			

Injection site erythema subjects affected / exposed occurrences (all)	2 / 243 (0.82%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	 18 / 243 (7.41%) 23 16 / 243 (6.58%) 17 9 / 243 (3.70%) 10 11 / 243 (4.53%) 11		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) Hyperlipidaemia subjects affected / exposed occurrences (all)	 3 / 243 (1.23%) 3 4 / 243 (1.65%) 4 2 / 243 (0.82%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2016	The significant changes to the protocol included: • The primary efficacy assessment and all secondary efficacy endpoints which previously planned to be assessed at Week 14 were moved from Week 14 to Week 12. • A new secondary efficacy endpoint, the percentage of subjects achieving low disease activity, defined as DAS28 (CRP) <3.2 was added. • One of the secondary efficacy endpoints was changed from the percentage of subjects with Simplified Disease Activity Index ≤3.3 evaluated at Week 24 to the percentage of subjects with CDAI ≤2.8 evaluated at Week 24. • The percentage of subjects with CDAI ≤2.8 at all other applicable time points and change from baseline to Weeks 12 and 24 in the Short Form 36 Mental Component Summary total score were added as other efficacy endpoints. • Folic acid was added as a required concomitant medication to counteract the potential side effects of MTX. • The prior use of all biologic disease-modifying anti-rheumatic drugs (including anakinra and abatacept) was made exclusionary. • Subjects with positive interferon-gamma release assay result at screening, or a history of untreated latent tuberculosis infection (LTBI) were allowed to enroll in the study if active tuberculosis was ruled out by a certified tuberculosis specialist or pulmonologist who was experienced in diagnosing and treating tuberculosis and in case of presence prophylactic treatment of LTBI. • Additional guidance for monitoring and reporting events of potential hepatotoxicity was added and potential hepatotoxicity events that fulfilled certain criteria were to be recorded as serious. • Guidance for the management of LTBI was added.
23 November 2016	The study protocol was amended to indicate that both the 0.4 mL and 0.8 mL prefilled syringes were to be used in the study. There were no changes to the conduct of the study as a result of this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported