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

Summary

EudraCT number	2015-005308-27
Trial protocol	CZ HU DE
Global end of trial date	01 October 2019

Results information

Result version number	v1 (current)
This version publication date	31 December 2020
First version publication date	31 December 2020

Trial information

Trial identification

Sponsor protocol code	CL04041025

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02760433
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	01 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Olokizumab (OKZ) 64 milligram (mg) administered subcutaneously (SC) once every 2 weeks (q2w) or once every 4 weeks (q4w) relative to placebo in subjects with moderately to severely active rheumatoid arthritis (RA) inadequately controlled by tumor necrosis factor alpha (TNF-α) 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 methotrexate (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	25 January 2017
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	Argentina: 28
Country: Number of subjects enrolled	Brazil: 24
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	Czechia: 36
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Mexico: 73
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	United States: 128
Worldwide total number of subjects	368
EEA total number of subjects	77

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)	300
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter Phase III study conducted at 123 study centers in 11 countries between 25 January 2017 and 01 October 2019. A total of 718 subjects were screened, of which 350 subjects were screen failures and 368 subjects were randomized in the study.

Pre-assignment

Screening details:

Subjects with moderately to severely active RA with an inadequate response to TNF-α inhibitor therapy for at least 12 weeks prior to Screening with ≥1 licensed TNF-α inhibitor were assessed for eligibility. Eligible subjects were randomized in 2:2:1 ratio to receive OKZ 64 mg q4w, OKZ 64 mg q2w, or placebo in 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	Investigator, Monitor, Assessor, Subject

Blinding implementation details:

Since the study treatments were distinguishable, they were prepared by the unblinded pharmacist (or their unblinded designee) out of sight of the subject and any blinded study team members. The study treatments were provided to blinded site staff in blinded syringes that were identical in appearance.

Arms

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

Arm description:

Subjects received an 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 20 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 an 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	Placebo

Arm description:

Subjects received an SC injection of Placebo q2w and stable dose of MTX. The last dose of placebo was at Week 14 of the Treatment Period from Week 0 to Week 24. Subjects were re-randomized in a blinded fashion to receive either OKZ 64 mg q4w alternating with placebo q4w or OKZ 64 mg q2w starting at Week 16 and continuing for the remainder of the double-blind Treatment Period. 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 or q4w by SC injection in either abdomen or thigh, prepared in blinded syringes of 0.4 mL.

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 or q2w OKZ 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	Placebo
Started	161	138	69
Received Treatment	161	138	69
Completed Week 16	139	129	58
Completed Treatment Period	136	127 [1]	57
Continued into Safety Follow-Up Period	14 [2]	9 [3]	8 [4]

Enrolled in OLE	127 [5]	124 [6]	51 [7]
Completed	134	128	56
Not completed	27	10	13
Consent withdrawn by subject	23	9	11
Other	3	1	1
Lost to follow-up	1	-	1

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 who discontinued treatment early and entered the safety follow-up period were considered completers for the whole study if they performed all 3 follow-up visits. Therefore, the number of subjects who completed study can be higher than number of treatment completers.

[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 who discontinued treatment early had to enter the safety follow-up period as well as subjects who completed treatment period; therefore, the numbers subjects enrolled in OLE and continued to the safety follow-up period are higher than those who completed treatment period.

[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 who discontinued treatment early had to enter the safety follow-up period as well as subjects who completed treatment period; therefore, the numbers subjects enrolled in OLE and continued to the safety follow-up period are higher than those who completed treatment period.

[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 who discontinued treatment early had to enter the safety follow-up period as well as subjects who completed treatment period; therefore, the numbers subjects enrolled in OLE and continued to the safety follow-up period are higher than those who completed treatment period.

[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 who discontinued treatment early had to enter the safety follow-up period as well as subjects who completed treatment period; therefore, the numbers subjects enrolled in OLE and continued to the safety follow-up period are higher than those who completed treatment period.

[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 who discontinued treatment early had to enter the safety follow-up period as well as subjects who completed treatment period; therefore, the numbers subjects enrolled in OLE and continued to the safety follow-up period are higher than those who completed treatment period.

[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 who discontinued treatment early had to enter the safety follow-up period as well as subjects who completed treatment period; therefore, the numbers subjects enrolled in OLE and continued to the safety follow-up period are higher than those who completed treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	OKZ 64 mg q4w

Reporting group description:

Subjects received an 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 20 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 an 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	Placebo

Reporting group description:

Subjects received an SC injection of Placebo q2w and stable dose of MTX. The last dose of placebo was at Week 14 of the Treatment Period from Week 0 to Week 24. Subjects were re-randomized in a blinded fashion to receive either OKZ 64 mg q4w alternating with placebo q4w or OKZ 64 mg q2w starting at Week 16 and continuing for the remainder of the double-blind Treatment Period. 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	Placebo
Number of subjects	161	138	69
Age categorical Units: Subjects			
Adults (18-64 years)	132	114	54
From 65-84 years	29	24	15
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.9	53.4	53.0
standard deviation	± 11.68	± 12.68	± 13.70
Gender categorical Units: Subjects			
Female	130	122	55
Male	31	16	14
Race Units: Subjects			
Asian	3	6	2
Black or African American	11	11	1
White	139	110	53
Other / Mixed	8	11	13
Ethnicity Units: Subjects			

Hispanic or Latino	77	64	42
Not Hispanic or Latino	84	74	27

Reporting group values	Total		
Number of subjects	368		
Age categorical Units: Subjects			
Adults (18-64 years)	300		
From 65-84 years	68		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	307		
Male	61		
Race Units: Subjects			
Asian	11		
Black or African American	23		
White	302		
Other / Mixed	32		
Ethnicity Units: Subjects			
Hispanic or Latino	183		
Not Hispanic or Latino	185		

End points

End points reporting groups

Reporting group title	OKZ 64 mg q4w

Reporting group description:

Subjects received an 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 20 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 an 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	Placebo

Reporting group description:

Subjects received an SC injection of Placebo q2w and stable dose of MTX. The last dose of placebo was at Week 14 of the Treatment Period from Week 0 to Week 24. Subjects were re-randomized in a blinded fashion to receive either OKZ 64 mg q4w alternating with placebo q4w or OKZ 64 mg q2w starting at Week 16 and continuing for the remainder of the double-blind Treatment Period. 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 American College of Rheumatology 20% Response Criteria (ACR20) at Week 12

End point title	Percentage of Subjects Meeting the American College of Rheumatology 20% Response Criteria (ACR20) at Week 12

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) Patient 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

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	161	138	69	
Units: Percentage of subjects				
number (not applicable)	59.6	60.9	40.6	

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	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [1]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.19
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.03
upper limit	0.337

Notes:

[1] - P-values are 1-sided p-values from 2x2 chi-square test, assessed for statistical significance at the alfa level of 0.0125. Confidence interval was calculated using Newcombe hybrid score method.

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	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029 [2]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.203
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.038
upper limit	0.353

Notes:

[2] - P-values are 1-sided p-values from 2x2 chi-square test, assessed for statistical significance at the alfa level of 0.0125. Confidence interval was calculated using Newcombe hybrid score method.

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 Patient Global Assessment of Disease Activity (VAS) (in millimeters) according to the formula:
DAS28 (CRP) = 0.56 × √(TJC) + 0.28 × √(SJC) + 0.36 × ln (CRP + 1) + 0.014 × Patient Global Assessment of Disease Activity (VAS) + 0.96.

The 28 joints evaluated for the SJC and TJC were: shoulders, elbows, wrists, interphalangeal on digit 1, proximal interphalangeals on digits 2 to 5, metacarpophalangeal on digits 1 to 5, and knees. A subject classed as having low disease activity who remained on randomized treatment and who were in the study at Week 12 and had a DAS28 (CRP) <3.2. 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	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	138	69	
Units: Percentage of subjects				
number (not applicable)	28.0	39.9	11.6	

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	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035 [3]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.164
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.029
upper limit	0.268

Notes:

[3] - P-values are 1-sided p-values from 2x2 chi-square test, assessed for statistical significance at the alfa level of 0.0125. Confidence interval was calculated using Newcombe hybrid score method.

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	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.283
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.139
upper limit	0.396

Notes:

[4] - P-values are 1-sided p-values from 2x2 chi-square test, assessed for statistical significance at the alfa level of 0.0125. Confidence interval was calculated using Newcombe hybrid score method.

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 impact of disease and its treatment on physical function. HAQ-DI assessed degree of difficulty experienced in 8 domains of daily living activities using 20 questions. For each question, 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 maximum score of each question. HAQ-DI was calculated by dividing sum of category scores by number of categories with at least 1 question answered. If fewer than 6 categories had responses, no disability score was calculated. 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 ITT population, which included all randomized subjects with Baseline and Week 12 HAQ-DI values.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

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	157	131	68	
Units: Units on HAQ-DI scale				
least squares mean (standard error)	-0.39 (± 0.044)	-0.49 (± 0.048)	-0.32 (± 0.068)	

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	225
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.1814 [6]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.07
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.26
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.081

Notes:

[5] - ANCOVA model included treatment as fixed effect and baseline value as a covariate. LSMs and P-value were obtained using Rubin's rule.
[6] - P-values represent a 1-sided combined test for treatment effect from the ANCOVA model, assessed for statistical significance at the alfa level of 0.0125.

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	199
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0227 [8]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.17
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.35
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.083

Notes:

[7] - ANCOVA model included treatment as fixed effect and baseline value as a covariate. LSMs and P-value were obtained using Rubin's rule.
[8] - P-values represent a 1-sided combined test for treatment effect from the ANCOVA model, assessed for statistical significance at the alfa level of 0.0125.

Secondary: Percentage of Subjects Achieving American College of Rheumatology 50% Response Criteria (ACR50) at Week 12

End point title	Percentage of Subjects Achieving American College of Rheumatology 50% Response Criteria (ACR50) at Week 12

End point description:

To meet ACR50 response criteria at Week 12, 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) Patient 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 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	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	138	69	
Units: Percentage of subjects				
number (not applicable)	32.3	33.3	15.9	

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	230
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0054 [10]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.164
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.02
upper limit	0.278

Notes:

[9] - Due to the hierarchy in the statistical gate-keeping strategy, the p-value cannot be used for formal inference because superiority was not shown for the HAQ-DI Improvement at Week 12 secondary endpoint.
[10] - P-values are 1-sided p-values from 2x2 chi-square test. Confidence interval was calculated using Newcombe hybrid score method.

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	207
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0041 [12]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.174
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.027
upper limit	0.294

Notes:

[11] - Due to the hierarchy in the statistical gate-keeping strategy, the p-value cannot be used for formal inference because superiority was not shown for the HAQ-DI Improvement at Week 12 secondary endpoint.

[12] - P-values are 1-sided p-values from 2x2 chi-square test. Confidence interval was calculated using Newcombe hybrid score method.

Secondary: Percentage of Subjects Achieving Remission, Defined as Clinical Disease Activity Index (CDAI) ≤2.8 (Remission) at Week 12

End point title	Percentage of Subjects Achieving Remission, Defined as Clinical Disease Activity Index (CDAI) ≤2.8 (Remission) at Week 12

End point description:

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

Subjects were classed as in remission if they remained on randomized treatment and in the study at Week 12 and with a CDAI of ≤2.8. Analysis was performed on the ITT population, which included all randomized subjects.

End point type	Secondary

End point timeframe:

At Week 12

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	161	138	69	
Units: Percentage of subjects				
number (not applicable)	3.1	6.5	0	

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	230
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.1619 [14]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.031
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.052
upper limit	0.083

Notes:

[13] - Due to the hierarchy in the statistical gate-keeping strategy, the p-value cannot be used for formal inference because superiority was not shown for the HAQ-DI Improvement at Week 12 secondary endpoint.
[14] - P-values are 1-sided p-values from 2x2 chi-square test. Confidence interval was calculated using Newcombe hybrid score method.

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	207
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0353 [16]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.065
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.023
upper limit	0.134

Notes:

[15] - Due to the hierarchy in the statistical gate-keeping strategy, the p-value cannot be used for formal inference because superiority was not shown for the HAQ-DI Improvement at Week 12 secondary endpoint.
[16] - P-values are 1-sided p-values from 2x2 chi-square test. Confidence interval was calculated using Newcombe hybrid score method.

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 an 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 20 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 an 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	Placebo

Reporting group description:

Subjects received an SC injection of Placebo q2w and stable dose of MTX. The last dose of placebo was at Week 14 of the Treatment Period from Week 0 to Week 24. Subjects were re-randomized in a blinded fashion to receive either OKZ 64 mg q4w alternating with placebo q4w or OKZ 64 mg q2w starting at Week 16 and continuing for the remainder of the double-blind Treatment Period. 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. TEAEs that occur after the first administration of placebo and prior to any administration of OKZ at or after Week 16 are summarized as a TEAE under placebo reporting group.

Reporting group title	Placebo - OKZ 64 mg q4w

Reporting group description:

Subjects received an SC injection of Placebo q2w and stable dose of MTX. The last dose of placebo was at Week 14 of the Treatment Period from Week 0 to Week 24. Subjects were re-randomized in a blinded fashion to receive OKZ 64 mg q4w alternating with placebo q4w starting at Week 16 and continuing for the remainder of the double-blind Treatment Period. 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. TEAEs that occur after the first administration of OKZ 64 mg q4w at or after Week 16 are summarized as a TEAE under Placebo-OKZ 64 mg q4w reporting group.

Reporting group title	Placebo - OKZ 64 mg q2w

Reporting group description:

Subjects received an SC injection of Placebo q2w and stable dose of MTX. The last dose of placebo was at Week 14 of the Treatment Period from Week 0 to Week 24. Subjects were re-randomized in a blinded fashion to receive OKZ 64 mg q2w starting at Week 16 and continuing for the remainder of the double-blind Treatment Period. 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. TEAEs that occur after the first administration of OKZ 64 mg q2w at or after Week 16 are summarized as a TEAE under Placebo-OKZ 64 mg q2w reporting group.

Serious adverse events	OKZ 64 mg q4w	OKZ 64 mg q2w	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 160 (3.75%)	12 / 139 (8.63%)	0 / 69 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 160 (0.63%)	0 / 139 (0.00%)	0 / 69 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Transaminases increased			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Ulna fracture			

subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 139 (0.00%)	0 / 69 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 139 (0.00%)	0 / 69 (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
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	1 / 160 (0.63%)	0 / 139 (0.00%)	0 / 69 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	1 / 160 (0.63%)	0 / 139 (0.00%)	0 / 69 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Osteoarthritis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 160 (0.63%)	1 / 139 (0.72%)	0 / 69 (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
Pilonidal cyst			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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
Pneumonia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 139 (0.00%)	0 / 69 (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
Sepsis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 139 (0.72%)	0 / 69 (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

Serious adverse events	Placebo - OKZ 64 mg q4w	Placebo - OKZ 64 mg q2w	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypertensive crisis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Intervertebral disc protrusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	OKZ 64 mg q4w	OKZ 64 mg q2w	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 160 (23.75%)	38 / 139 (27.34%)	16 / 69 (23.19%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 160 (8.13%)	10 / 139 (7.19%)	0 / 69 (0.00%)
occurrences (all)	16	13	0
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 160 (5.00%)	9 / 139 (6.47%)	1 / 69 (1.45%)
occurrences (all)	9	10	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 160 (0.63%)	4 / 139 (2.88%)	3 / 69 (4.35%)
occurrences (all)	2	4	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 160 (0.63%)	1 / 139 (0.72%)	4 / 69 (5.80%)
occurrences (all)	1	1	4
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	7 / 160 (4.38%)	1 / 139 (0.72%)	0 / 69 (0.00%)
occurrences (all)	13	4	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 160 (1.88%)	6 / 139 (4.32%)	0 / 69 (0.00%)
occurrences (all)	4	6	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 160 (4.38%)	9 / 139 (6.47%)	1 / 69 (1.45%)
occurrences (all)	7	9	1
Upper respiratory tract infection			
subjects affected / exposed	6 / 160 (3.75%)	5 / 139 (3.60%)	4 / 69 (5.80%)
occurrences (all)	6	6	4
Latent tuberculosis			
subjects affected / exposed	6 / 160 (3.75%)	4 / 139 (2.88%)	0 / 69 (0.00%)
occurrences (all)	6	4	0
Influenza			

subjects affected / exposed	0 / 160 (0.00%)	5 / 139 (3.60%)	4 / 69 (5.80%)
occurrences (all)	0	5	4

Non-serious adverse events	Placebo - OKZ 64 mg q4w	Placebo - OKZ 64 mg q2w	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 26 (7.69%)	8 / 32 (25.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 26 (3.85%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 32 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Latent tuberculosis			

subjects affected / exposed	1 / 26 (3.85%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Influenza			
subjects affected / exposed	0 / 26 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	

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. • Subjects who were identified as nonresponders at Week 14 were assigned rescue medication starting at or as close as possible to Week 14, rather than starting at Week 16. • One of the secondary efficacy endpoints was changed from percentage of subjects with Simplified Disease Activity Index ≤3.3 to percentage of subjects with CDAI ≤2.8. • 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 new other efficacy endpoints. • The definition of moderate response in the other efficacy endpoint assessing the proportion of subjects with moderate to good response based on DAS28 (CRP) was revised to DAS28 (CRP) ≤5.1 with an improvement from baseline in DAS28 (CRP) >0.6 and ≤1.2, or DAS28 (CRP) >3.2 with an improvement from baseline in DAS28 (CRP) >1.2. • A study visit at Week 17 was deleted from the study. • Folic acid was added as a required concomitant medication to counteract the potential side-effects of MTX. • Subjects with a 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 experienced in diagnosing and treating tuberculosis, subject completed at least 30 days of LTBI therapy prior to randomization, and subject agreed to complete the recommend course of LTBI therapy. • 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. • Additional guidance for the management of LTBI was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported