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 Methotrexate Therapy

Summary

EudraCT number	2014-004719-36
Trial protocol	BG
Global end of trial date	29 April 2019

Results information

Result version number	v1 (current)
This version publication date	07 May 2020
First version publication date	07 May 2020

Trial information

Trial identification

Sponsor protocol code	CL04041022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02760368
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	29 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of Olokizumab (OKZ) 64 milligrams (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 methotrexate (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:

All subjects continued to receive their prior background therapy (MTX) during the study.

In accordance with the inclusion criteria, subjects must have been treated with MTX at a dose of 15 to 25 mg/week (or ≥10 mg/week if there was documented intolerance to higher doses) for at least 12 weeks prior to Screening with a stable dose and an unchanged mode of administration (oral, SC, or intramuscular [IM]) for at least 6 weeks prior to Screening.

The dose of background MTX was to remain unchanged throughout the study but could be adjusted once during the study and only for safety reasons according to the Investigator’s discretion.

Concomitant treatment with folic acid ≥5 mg per week or equivalent was required for all subjects starting by Visit 2 (Week 0). Folic acid or equivalent was not to be taken on the same day as MTX.

Evidence for comparator: -

Actual start date of recruitment	19 May 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	Belarus: 20
Country: Number of subjects enrolled	Bulgaria: 27
Country: Number of subjects enrolled	Russian Federation: 381
Worldwide total number of subjects	428
EEA total number of subjects	27

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)	378
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study running between 19 May 2016 and 29 April 2019. Four hundred and twenty eight subjects in 3 countries (Belarus, Russian Federation and Bulgaria) were eligible to enter the study and receive treatment.

Pre-assignment

Screening details:

Subjects with moderately to severely active, adult onset, RA disease with an inadequate response to treatment with oral, SC, or IM MTX for at least 12 weeks prior to Screening were assessed for eligibility. Eligible subjects were randomized in a 1:1:1 ratio to receive 64 mg OKZ q2w, 64 mg OKZ q4w, or placebo for 24 weeks.

Period 1

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

Blinding implementation details:

The placebo differed in appearance from OKZ, and was prepared by independent unblinded pharmacist or designee and provided to the blinded site staff in blinded syringes.

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. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period at Week 22, subjects could enter an 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	OKZ
Other name	
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 q4w (alternating with OKZ 64 mg q4w, in order to maintain the blinding). Placebo (sodium chloride 0.9%) was administered 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. All subjects continued to receive MTX during the

study. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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	OKZ
Other name	
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 a SC injection of placebo q2w. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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	Placebo
Started	142	143	143
Completed Treatment	131 [1]	129 [2]	134
Continued into Safety Follow Up	7 [3]	13 [4]	8 [5]
Enrolled in OLE Study	127 [6]	122 [7]	126 [8]
Completed	134	130	132
Not completed	8	13	11
Consent withdrawn by subject	8	12	9
Withdrawal by Sponsor	-	-	1
Death	-	1	-
Screen failure	-	-	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 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.

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. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period at Week 22, subjects could enter an 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. All subjects continued to receive MTX during the study. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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	142	143	143
Age categorical Units: Subjects			
Adults (18-64 years)	129	125	124
From 65-84 years	13	18	19
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	49.1	52.0	52.7
standard deviation	± 12.07	± 11.77	± 11.29
Gender categorical Units: Subjects			
Female	118	116	120
Male	24	27	23
Race Units: Subjects			
Asian	0	0	1
Black or African American	0	0	0
White	142	143	142
Other / Mixed	0	0	0

Reporting group values	Total		
Number of subjects	428		
Age categorical Units: Subjects			
Adults (18-64 years)	378		

From 65-84 years	50		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	354		
Male	74		
Race			
Units: Subjects			
Asian	1		
Black or African American	0		
White	427		
Other / Mixed	0		

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. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period at Week 22, subjects could enter an 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. All subjects continued to receive MTX during the study. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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) 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

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	142	143	143	
Units: Percentage of subjects				
number (not applicable)	70.4	63.6	25.9	

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	285
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.445
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.318
upper limit	0.552

Notes:

[1] - Confidence Interval was calculated using Newcombe hybrid score method.

[2] - P-value was 1-sided p-value 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	286
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.378
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.248
upper limit	0.489

Notes:

[3] - Confidence Interval was calculated using Newcombe hybrid score method.

[4] - P-value was 1-sided p-value from 2x2 chi-square test.

Secondary: Percentage of Subjects with Disease Activity Score 28-Joint Count CRP (DAS 28 [CRP]) <3.2 at Week 12

End point title	Percentage of Subjects with 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 × √(TJC) + 0.28 × √(SJC) + 0.36 × ln (CRP + 1) + 0.014 × 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	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	143	143	
Units: Percentage of Subjects				
number (not applicable)	38.7	33.6	3.5	

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	285
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.352
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.251
upper limit	0.449

Notes:

[5] - Confidence Interval was calculated using Newcombe hybrid score method.

[6] - P-value was 1-sided p-value 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	286
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.301
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.203
upper limit	0.396

Notes:

[7] - Confidence Interval was calculated using Newcombe hybrid score method.

[8] - P-value was 1-sided p-value from 2x2 chi-square test.

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	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	141	140	
Units: Units on HAQ-DI scale				
least squares mean (standard error)	-0.56 (± 0.042)	-0.54 (± 0.041)	-0.20 (± 0.042)	

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	282
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.36
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.49
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

[9] - ANCOVA model included treatment as fixed effect and Baseline value as a covariate. LSMs and P-value were obtained using Rubins's rule.
[10] - P-value represents 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	Placebo v OKZ 64 mg q2w
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	ANCOVA
Parameter estimate	LSM difference
Point estimate	-0.34
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.47
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

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

Secondary: Percentage of Subjects Achieving an ACR50 response at Week 24

End point title	Percentage of Subjects Achieving an ACR50 response 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	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	143	143	
Units: Percentage of Subjects				
number (not applicable)	48.6	42.7	7.7	

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	285
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.409
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.296
upper limit	0.509

Notes:
[13] - Confidence Interval was calculated using Newcombe hybrid score method.
[14] - P-value was 1 sided p-value 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	286
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.35
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.239
upper limit	0.45

Notes:
[15] - Confidence Interval was calculated using Newcombe hybrid score method.

[16] - P-value was 1 sided p-value from 2x2 chi-square test.

Secondary: Percentage of Subjects with Clinical Disease Activity Index (CDAI) ≤2.8 (remission) at Week 24

End point title	Percentage of Subjects with 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 mm) 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	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	143	143	
Units: Percentage of Subjects				
number (not applicable)	7.7	8.4	0.0	

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	285
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0003 [18]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.077
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.027
upper limit	0.143

Notes:

[17] - Confidence Interval was calculated using Newcombe hybrid score method.

[18] - P-value was 1-sided p-value 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	286
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0002 [20]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.084
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.032
upper limit	0.151

Notes:

[19] - Confidence Interval was calculated using Newcombe hybrid score method.

[20] - P-value was 1-sided p-value from 2x2 chi-square test.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were recorded after the first dose of the study treatment until 22 weeks after the last dose of study treatment (a total of 44 weeks).

Adverse event reporting additional description:

The safety population included all subjects who received at least 1 dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

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 injection of placebo q4w to maintain blinding. All subjects continued to receive MTX during the study.After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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. All subjects continued to receive MTX during the study. After completion of the double-blind Treatment Period with at Week 22, subjects could enter an 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	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 142 (5.63%)	8 / 143 (5.59%)	4 / 142 (2.82%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 142 (2.82%)	2 / 143 (1.40%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	5 / 5	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	3 / 142 (2.11%)	0 / 143 (0.00%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage II			
subjects affected / exposed	1 / 142 (0.70%)	0 / 143 (0.00%)	0 / 142 (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
Vascular disorders			
Diabetic vascular disorder			
subjects affected / exposed	1 / 142 (0.70%)	0 / 143 (0.00%)	0 / 142 (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
Nervous system disorders			
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 142 (0.70%)	0 / 143 (0.00%)	0 / 142 (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			
Obstructive pancreatitis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 143 (0.00%)	0 / 142 (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			
Drug-induced liver injury			
subjects affected / exposed	1 / 142 (0.70%)	0 / 143 (0.00%)	0 / 142 (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
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	0 / 142 (0.00%)	1 / 143 (0.70%)	0 / 142 (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
Musculoskeletal and connective tissue disorders			

Rheumatoid arthritis			
subjects affected / exposed	0 / 142 (0.00%)	2 / 143 (1.40%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula			
subjects affected / exposed	1 / 142 (0.70%)	0 / 143 (0.00%)	0 / 142 (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
Infections and infestations			
Subcutaneous abscess			
subjects affected / exposed	0 / 142 (0.00%)	2 / 143 (1.40%)	0 / 142 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 142 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 142 (0.00%)	0 / 143 (0.00%)	1 / 142 (0.70%)
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	0 / 142 (0.00%)	1 / 143 (0.70%)	0 / 142 (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
Staphylococcal sepsis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 143 (0.70%)	0 / 142 (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
Toxic shock syndrome			
subjects affected / exposed	0 / 142 (0.00%)	1 / 143 (0.70%)	0 / 142 (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

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	53 / 142 (37.32%)	51 / 143 (35.66%)	35 / 142 (24.65%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	30 / 142 (21.13%)	25 / 143 (17.48%)	11 / 142 (7.75%)
occurrences (all)	24	32	14
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 142 (13.38%)	16 / 143 (11.19%)	10 / 142 (7.04%)
occurrences (all)	27	22	12
White blood cell count decreased			
subjects affected / exposed	6 / 142 (4.23%)	7 / 143 (4.90%)	4 / 142 (2.82%)
occurrences (all)	13	9	5
Neutrophil count decreased			
subjects affected / exposed	7 / 142 (4.93%)	6 / 143 (4.20%)	3 / 142 (2.11%)
occurrences (all)	10	6	4
Blood cholesterol increased			
subjects affected / exposed	4 / 142 (2.82%)	6 / 143 (4.20%)	3 / 142 (2.11%)
occurrences (all)	4	7	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 142 (4.23%)	3 / 143 (2.10%)	4 / 142 (2.82%)
occurrences (all)	9	5	5
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	7 / 142 (4.93%)	8 / 143 (5.59%)	4 / 142 (2.82%)
occurrences (all)	10	10	4
Neutropenia			
subjects affected / exposed	9 / 142 (6.34%)	5 / 143 (3.50%)	2 / 142 (1.41%)
occurrences (all)	11	6	2
Anaemia			
subjects affected / exposed	3 / 142 (2.11%)	4 / 143 (2.80%)	6 / 142 (4.23%)
occurrences (all)	3	4	9
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	3 / 142 (2.11%)	4 / 143 (2.80%)	6 / 142 (4.23%)
occurrences (all)	3	4	8
Upper respiratory tract infection			
subjects affected / exposed	6 / 142 (4.23%)	2 / 143 (1.40%)	4 / 142 (2.82%)
occurrences (all)	9	2	4

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 2 of the secondary efficacy endpoints (DAS28 [CRP] and HAQ-DI) were moved from Week 14 to Week 12. • 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 additional 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. • The requirement that subjects must be anti-citrullinated protein antibody positive or rheumatoid factor positive at Screening was removed as an inclusion criterion. • The prior use of all biologic disease-modifying anti-rheumatic drugs was made exclusionary. • Subjects with a history of no response to the rescue medications used in this study were excluded. • Subjects with positive interferon-gamma release assay result, history of latent tuberculosis infection (LTBI) or who developed LTBI during the study were allowed to begin or continue study treatment if active tuberculosis was ruled out and the subject has started and agreed to complete the recommend course of LTBI therapy. • Additional guidance for monitoring and reporting hepatotoxicity events was added and potential hepatotoxicity events that fulfilled certain criteria were to be recorded as serious.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 June 2016	After 1 subject was randomized in Bulgaria, the sponsor temporarily suspended the trial as data indicated that the Investigational Product was out of specification. The 1 subject was removed from the trial. Subject enrolment was reinitiated in all sites beginning on 10 Jan 2017.	10 January 2017

Notes:

Limitations and caveats

None reported