Clinical trial results:
A Multicenter, Open-Label, Phase III Study of the Efficacy and Safety of Olokizumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis

Summary

EudraCT number	2015-005309-35
Trial protocol	GB DE LT CZ HU PL BG LV
Global end of trial date	01 September 2021

Results information

Result version number	v1 (current)
This version publication date	24 July 2022
First version publication date	24 July 2022

Trial information

Trial identification

Sponsor protocol code	CL04041024

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03120949
WHO universal trial number (UTN)	-
Other trial identifiers	IND : 104933

Notes:

Sponsors

Sponsor organisation name	R-Pharm International, LLC
Sponsor organisation address	19, building 1, Berzarina Street, Moscow, Russian Federation, 123154
Public contact	Medical Department, R-Pharm International LLC, +7 495 956 7937,
Scientific contact	Medical Department, R-Pharm International LLC, +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 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of olokizumab (OKZ) 64 milligram (mg) administered subcutaneously (SC) once every 2 weeks (q2w) or once every 4 weeks (q4w) in subjects with moderately to severely active rheumatoid arthritis (RA) who previously completed 24 weeks of double-blind treatment in the core studies (CL04041022, CL04041023, or CL04041025).

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:

For the first 12 weeks of the open-label extension (OLE), all subjects were required to remain on a stable dose of background methotrexate (MTX) at 15 to 25 mg/week (or≥10 mg/week if there was documented intolerance to higher doses) with a stable route of administration (oral, SC, or intramuscular [IM]). After 12 weeks (Visit 4 [Week 36] of the OLE study), the Investigator might adjust the MTX dosage and route, per local guidelines. MTX might be adjusted only for safety reasons according to Investigator discretion before Visit 4 (Week 36) of the OLE study. Subjects who had been on rescue disease-modifying anti-rheumatic drugs during the core studies were asked to continue these medications for the first 12 weeks of the OLE study. The Investigator could adjust these background medications if deemed appropriate after Visit 4 (Week 36) of the OLE study. Background rescue therapy might be adjusted only for safety reasons according to Investigator discretion before Visit 4 (Week 36) of the OLE study. Folic acid ≥5 mg per week or equivalent was required during the study.

Evidence for comparator: -

Actual start date of recruitment	04 July 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: 154
Country: Number of subjects enrolled	Belarus: 18
Country: Number of subjects enrolled	Bulgaria: 77
Country: Number of subjects enrolled	Brazil: 116
Country: Number of subjects enrolled	Colombia: 64
Country: Number of subjects enrolled	Czechia: 199
Country: Number of subjects enrolled	Estonia: 9
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Hungary: 67
Country: Number of subjects enrolled	Lithuania: 67

Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Mexico: 264
Country: Number of subjects enrolled	Poland: 271
Country: Number of subjects enrolled	Russian Federation: 425
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 306
Worldwide total number of subjects	2105
EEA total number of subjects	729

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)	1727
From 65 to 84 years	377
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This was a multicenter, open-label Phase III conducted at 241 study centers. Subjects with moderately to severely active RA who previously completed 24 weeks of double-blinded treatment in the core studies (CL04041022, CL04041023, or CL04041025) assessed for eligibility to enter this study.

Pre-assignment

Screening details:

A total of 2105 subjects were randomized in this OLE study, of which 2104 subjects received the study drug. One subject was randomized in error and did not receive any dose of study drug.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

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

Arm description:

OKZ 64 mg q4w (OLE) group includes all subjects who received OKZ 64 mg q4w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q4w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the end of treatment (EoT) Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

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 OKZ 64 mg q4w as SC injection.

Arm title	OKZ 64 mg q2w (OLE)

Arm description:

OKZ 64 mg q2w (OLE) group includes all subjects who received OKZ 64 mg q2w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q2w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the EoT Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Arm type	Experimental

Investigational medicinal product name	Olokizumab
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Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received OKZ 64 mg q2w as SC injection.

Number of subjects in period 1	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)
Started	1058	1047
Received Treatment	1057	1047
Completed	830	842
Not completed	228	205
Randomized in error	1	-
Consent withdrawn by subject	139	124
Death	13	13
Unspecified	52	55
Lost to follow-up	23	13

Baseline characteristics

Reporting groups	
Reporting group title	OKZ 64 mg q4w (OLE)

Reporting group description:

OKZ 64 mg q4w (OLE) group includes all subjects who received OKZ 64 mg q4w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q4w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the end of treatment (EoT) Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Reporting group title	OKZ 64 mg q2w (OLE)

Reporting group description:

OKZ 64 mg q2w (OLE) group includes all subjects who received OKZ 64 mg q2w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q2w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the EoT Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Reporting group values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)	Total
Number of subjects	1058	1047	2105
Age categorical Units: Subjects			
Adults (18-64 years)	863	864	1727
From 65-84 years	195	182	377
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	851	840	1691
Male	207	207	414
Race Units: Subjects			
Asian	15	17	32
Black or African American	31	46	77
White	915	896	1811
Other / Mixed	97	88	185
EthnicityHispanic or Latino Units: Subjects			
Hispanic or Latino	358	332	690
Not Hispanic or Latino	700	715	1415

End points

End points reporting groups

Reporting group title	OKZ 64 mg q4w (OLE)

Reporting group description:

OKZ 64 mg q4w (OLE) group includes all subjects who received OKZ 64 mg q4w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q4w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the end of treatment (EoT) Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Reporting group title	OKZ 64 mg q2w (OLE)

Reporting group description:

OKZ 64 mg q2w (OLE) group includes all subjects who received OKZ 64 mg q2w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q2w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the EoT Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Subject analysis set title	OKZ 64 mg q4w (OLE)
Subject analysis set type	Safety analysis

Subject analysis set description:

OKZ 64 mg q4w (OLE) group includes all subjects who received OKZ 64 mg q4w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q4w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the EoT Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Subject analysis set title	OKZ 64 mg q2w (OLE)
Subject analysis set type	Safety analysis

Subject analysis set description:

OKZ 64 mg q2w (OLE) group includes all subjects who received OKZ 64 mg q2w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q2w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the EoT Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAE), Serious TEAEs and Adverse Events of Special Interest (AESI)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAE), Serious TEAEs and Adverse Events of Special Interest (AESI)[1]

End point description:

TEAEs was defined as AEs that first occurred or worsened in severity on or after the first administration of the OLE study treatment. These safety concerns were identified as AESIs: infections (tuberculosis and opportunistic infections); malignancies; elevation of blood lipids; systemic injection reactions and hypersensitivity reactions; gastrointestinal perforation; cardiovascular events; neutropenia, thrombocytopenia, leukocytopenia, and pancytopenia; hepatotoxicity; injection site reactions; demyelination in peripheral or central nervous system and autoimmune disorders. The causal relationship between the study treatment and the AEs was characterized as "not related" or "related".

The severity of AEs was characterized as per Common Terminology Criteria for AEs (CTCAE) as grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life threatening consequences; grade 5: death. Safety population included all subjects who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1043	1061		
Units: subjects				
number (not applicable)				
Any TEAE	753	793		
Any Serious TEAE	129	120		
TEAE of Special Interest	598	611		
TEAE Related to Study Treatment	318	352		
TEAE with Grade 3 Severity	168	163		
TEAE with Grade 4 Severity	5	8		
TEAE with Grade 5 Severity	13	13		

Statistical analyses

No statistical analyses for this end point

Primary: Follow-up-Adjusted Incidence Rate of Serious TEAE and Treatment-Emergent AESI

End point title	Follow-up-Adjusted Incidence Rate of Serious TEAE and Treatment-Emergent AESI[2]

End point description:

Incidence rates for serious TEAE and treatment-emergent AESI were summarized per 100 subject-year (SY) of follow-up (/100 SY). The incidence rate was calculated as the number of subjects with an AE/ sum of the follow-up time (in 100 SY) over all subjects in each treatment group. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study.

End point type	Primary

End point timeframe:

From the day of the first dose of study treatment up to 22 weeks after the final dose of study treatment, approximately up to 102 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1043	1061		
Units: Subjects with an AE per 100 SY				
number (not applicable)				
SAE	7.74	7.37		
AESI	40.49	42.13		

Statistical analyses

No statistical analyses for this end point

Primary: Follow-up-adjusted Event Rates of Serious TEAE and Treatment-Emergent AESI

End point title	Follow-up-adjusted Event Rates of Serious TEAE and Treatment-Emergent AESI[3]

End point description:

Event rates for serious TEAE and treatment-emergent AESI were summarized per 100 SY of follow-up (/100 SY). Event rate per 100 SY was calculated as sum of the number of events that subject experienced under treatment/ total follow-up time (in 100-year units) of subject. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study.

End point type	Primary

End point timeframe:

From the day of the first dose of study treatment up to 80 weeks after the final dose of study treatment, approximately up to 102 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1043	1061		
Units: Events per 100 SY				
number (not applicable)				
SAE	9.48	10.24		
AESI	126.52	136.52		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Clinically Significant Abnormalities in Hematology, Clinical Chemistry Parameters

End point title	Percentage of Subjects with Clinically Significant Abnormalities in Hematology, Clinical Chemistry Parameters[4]

End point description:

Abnormal hematology assessments during OLE included hemoglobin <= 80 gram/liter (g/L); leukocytes

<3.5x 10^9/L; lymphocytes <500 x 10^6/L; neutrophils <1000 x 10^6/L and platelets <100 x 10^9/L. Abnormal chemistry assessments during OLE included alanine aminotransferase (ALT) >=3 x upper limit of normal (ULN), aspartate aminotransferase >=3 x ULN, and creatinine >= 177 micromoles per liter (mcmol/L) for males and >= 132 mcmol/L for females. Here, data for any time post-OLE baseline is reported. Any Time post-OLE baseline summarized all post-baseline values, including unscheduled assessments. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study.

End point type	Primary

End point timeframe:

Any Time Post-OLE Baseline, approximately 102 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1043	1061		
Units: percentage of subjects				
number (not applicable)				
Hemoglobin	0.7	0.3		
Leukocytes	17.1	17.2		
Lymphocytes	2.1	2.3		
Neutrophils	2.0	2.5		
Platelets	1.2	1.9		
ALT	8.9	9.0		
AST	4.0	3.8		
Creatinine	2.2	1.1		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline of Leukocytes, Lymphocytes, Neutrophils, and Platelets

End point title	Change from Baseline of Leukocytes, Lymphocytes, Neutrophils, and Platelets[5]

End point description:

Blood samples were collected for assessments of hematology parameters like leukocytes, lymphocytes, neutrophils, and platelets. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	974	1008		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Leukocytes: Week 2 (n=974, 1008)	-0.37 (± 1.779)	-0.42 (± 1.699)		
Leukocytes: Week 82 (n=817, 867)	-0.64 (± 1.974)	-0.67 (± 2.026)		
Leukocytes: Week 102 (n=48, 45)	0.22 (± 2.013)	0.18 (± 2.283)		
Lymphocytes: Week 2 (n=963, 995)	0.109 (± 0.5374)	0.098 (± 0.4870)		
Lymphocytes: Week 82 (n=811, 859)	-0.212 (± 0.5515)	-0.193 (± 0.5281)		
Lymphocytes: Week 102 (n=46, 45)	-0.160 (± 0.4854)	-0.069 (± 0.4961)		
Neutrophils: Week 2 (n=963, 995)	-0.520 (± 1.6813)	-0.542 (± 1.6010)		
Neutrophils: Week 82 (n=811, 859)	-0.428 (± 1.8352)	-0.467 (± 1.9113)		
Neutrophils: Week 102 (n=46, 45)	0.358 (± 1.8996)	0.136 (± 2.2672)		
Platelets: Week 2 (n=974, 1007)	-15.7 (± 47.62)	-19.0 (± 44.99)		
Platelets: Week 82 (n=811, 858)	-21.9 (± 58.46)	-25.1 (± 60.07)		
Platelets: Week 102 (n=46, 44)	-1.5 (± 57.07)	2.3 (± 74.21)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline of Hemoglobin

End point title	Change from Baseline of Hemoglobin[6]

End point description:

Blood samples were collected for assessments of hematology parameter like hemoglobin. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	982	1016		
Units: g/L				
arithmetic mean (standard deviation)				
Week 2 (n=982, 1016)	0.3 (± 6.42)	0.0 (± 7.46)		
Week 82 (n=817, 870)	4.1 (± 10.97)	3.6 (± 11.53)		
Week 102 (n=48, 45)	-1.0 (± 10.18)	2.1 (± 14.10)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in ALT, AST, and Gamma- Glutamyl Transferase (GGT)

End point title	Change from Baseline in ALT, AST, and Gamma- Glutamyl Transferase (GGT)[7]

End point description:

Blood samples were collected for assessments of chemistry parameters like ALT, AST and GGT. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	990	1024		
Units: U/L				
arithmetic mean (standard deviation)				
ALT: Week 2 (n=989, 1023)	4.2 (± 21.16)	3.8 (± 17.77)		
ALT: Week 82 (n=829, 885)	3.5 (± 24.21)	3.0 (± 27.87)		
ALT: Week 102 (n=47, 47)	-4.1 (± 17.79)	1.7 (± 15.65)		
AST: Week 2 (n=989, 1023)	1.8 (± 13.90)	2.4 (± 11.62)		
AST: Week 82 (n=829, 883)	2.6 (± 16.64)	2.3 (± 16.70)		
AST: Week 102 (n=46, 47)	-1.5 (± 11.76)	0.6 (± 12.09)		
GGT: Week 2 (n=990, 1024)	-0.3 (± 11.79)	0.4 (± 11.55)		
GGT: Week 82 (n=832, 885)	5.8 (± 36.65)	5.2 (± 30.40)		
GGT: Week 102 (n=48, 47)	5.8 (± 31.71)	4.3 (± 25.25)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Alkaline Phosphatase (ALP)

End point title	Change from Baseline in Alkaline Phosphatase (ALP)[8]

End point description:

Blood samples were collected for assessments of chemistry parameter like ALP. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	989	1024		
Units: IU/L				
arithmetic mean (standard deviation)				
Week 2 (n=989, 1024)	-4.8 (± 12.55)	-3.5 (± 10.11)		
Week 82 (n=830, 884)	-2.2 (± 22.87)	-3.0 (± 20.68)		
Week 102 (n=47, 47)	4.5 (± 21.76)	0.5 (± 18.35)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Bilirubin and Creatinine

End point title	Change from Baseline in Bilirubin and Creatinine[9]

End point description:

Blood samples were collected for assessments of chemistry parameters like bilirubin and creatinine. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	990	1024		
Units: mcmol/L				
arithmetic mean (standard deviation)				
Bilirubin: Week 2 (n=987, 1022)	0.6 (± 3.92)	0.6 (± 3.56)		
Bilirubin: Week 82 (n=827, 884)	1.2 (± 4.89)	1.3 (± 4.82)		
Bilirubin: Week 102 (n=46, 47)	-0.4 (± 3.14)	0.5 (± 5.15)		
Creatinine: Week 2 (n= 990, 1024)	1.1 (± 8.10)	1.1 (± 9.17)		
Creatinine: Week 82 (n=832, 885)	2.3 (± 10.24)	2.2 (± 12.50)		
Creatinine: Week 102 (n=48, 47)	0.3 (± 10.35)	1.7 (± 8.16)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Apolipoprotein A1 and Apolipoprotein B

End point title	Change From Baseline in Apolipoprotein A1 and Apolipoprotein B[10]

End point description:

Blood samples were collected for assessments of lipid parameters like apolipoprotein A1 and apolipoprotein B. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	942	979		
Units: g/L				
arithmetic mean (standard deviation)				
Apolipoprotein A1: Week 28 (n=942, 979)	0.024 (± 0.2472)	0.034 (± 0.2556)		
Apolipoprotein A1: Week 82 (n=829, 882)	0.001 (± 0.2437)	0.010 (± 0.2849)		
Apolipoprotein A1: Week 102 (n=40, 40)	-0.066 (± 0.2543)	-0.030 (± 0.3501)		
Apolipoprotein B: Week 28 (n=942, 979)	0.024 (± 0.2255)	0.012 (± 0.2198)		
Apolipoprotein B: Week 82 (n=829, 882)	0.023 (± 0.2405)	0.021 (± 0.2434)		
Apolipoprotein B: Week 102 (n=40, 40)	0.000 (± 0.2756)	0.010 (± 0.2305)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Low-density Lipoprotein (LDL) and High-density Lipoprotein (HDL) Cholesterol and Triglycerides

End point title	Change From Baseline in Low-density Lipoprotein (LDL) and High-density Lipoprotein (HDL) Cholesterol and Triglycerides[11]

End point description:

Blood samples were collected for assessments of lipid parameters like HDL and LDL cholesterol and triglycerides. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	941	979		
Units: mmol/L				
arithmetic mean (standard deviation)				
HDL Cholesterol: Week 28 (n=941, 979)	0.001 (± 0.2899)	0.006 (± 0.3013)		
HDL Cholesterol: Week 82 (n=826, 880)	-0.025 (± 0.3037)	-0.015 (± 0.3419)		
HDL Cholesterol: Week 102 (n=40, 40)	-0.055 (± 0.3666)	-0.122 (± 0.4506)		
LDL Cholesterol: Week 28 (n=941, 979)	0.104 (± 0.8213)	0.070 (± 0.8194)		
LDL Cholesterol: Week 82 (n=826, 880)	0.082 (± 0.8940)	0.092 (± 0.8819)		
LDL Cholesterol: Week 102 (n=40, 40)	0.003 (± 0.9175)	-0.034 (± 0.8752)		
Triglycerides: Week 28 (n=941, 979)	0.106 (± 0.8744)	0.071 (± 0.9075)		
Triglycerides: Week 82 (n=826, 880)	0.140 (± 0.9613)	0.128 (± 1.0187)		
Triglycerides: Week 102 (n=40, 40)	-0.260 (± 0.6176)	0.202 (± 0.6657)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Lipoprotein-a

End point title	Change From Baseline in Lipoprotein-a[12]

End point description:

Blood samples were collected for assessments of lipid parameter like Lipoprotein-a. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	937	967		
Units: nanomoles per liter				
arithmetic mean (standard deviation)				
Week 28 (n=937, 967)	-7.07 (± 25.882)	-7.29 (± 30.187)		
Week 82 (n=821, 878)	-6.51 (± 24.097)	-6.78 (± 36.699)		
Week 102 (n=40, 40)	0.65 (± 23.491)	2.45 (± 71.475)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Urinalysis Parameter: pH

End point title	Change From Baseline in Urinalysis Parameter: pH[13]

End point description:

Urine samples were collected at specified timepoints for evaluation of urine pH. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	982	1006		
Units: pH				
arithmetic mean (standard deviation)				
Week 12 (n=982, 1006)	-0.05 (± 0.685)	-0.02 (± 0.661)		
Week 82 (n=817, 872)	-0.04 (± 0.757)	-0.03 (± 0.765)		
Week 102 (n=38, 39)	-0.04 (± 0.586)	-0.10 (± 0.926)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Urinalysis Parameter: Specific Gravity

End point title	Change From Baseline in Urinalysis Parameter: Specific

End point description:

Urine samples were collected specified timepoints for assessment of specific gravity. Baseline was defined as the last available measurement prior to the first OLE dose of study treatment. Change from baseline was calculated as test value at visit minus baseline value. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	982	1006		
Units: ratio				
arithmetic mean (standard deviation)				
Week 12 (n=982, 1006)	0.0005 (± 0.00734)	0.0001 (± 0.00723)		
Week 82 (n=817, 872)	0.0000 (± 0.00759)	0.0000 (± 0.00766)		
Week 102 (n=38, 39)	0.0014 (± 0.00820)	0.0012 (± 0.00792)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Clinically Significant Abnormal Physical Examination

End point title	Number of Subjects with Clinically Significant Abnormal Physical Examination[15]

End point description:

A complete physical examination included evaluation of general appearance, skin, head, eyes, ears, nose and throat, respiratory, cardiovascular, gastrointestinal (GI) including hepatobiliary assessment, musculoskeletal, neurological systems, and urogenital system. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1003	1032		
Units: subjects				
number (not applicable)				
General Appearance: Week 2 (n=991, 1031)	4	1		
General Appearance: Week 82 (n=834, 899)	2	4		
General Appearance: Week 102 (n=49, 46)	0	0		
Skin: Week 2 (n=997, 1032)	4	6		
Skin: Week 82 (n=834, 898)	15	13		
Skin: Week 102 (n=49, 46)	1	1		
Respiratory: Week 2 (n=997, 1032)	2	3		
Respiratory: Week 82 (n=834, 899)	2	4		
Respiratory: Week 102 (n=49, 46)	0	0		
Cardiovascular: Week 2 (n=1003, 1025)	0	0		
Cardiovascular: Week 82 (n=834, 899)	4	0		
Cardiovascular: Week 102 (n=49, 46)	0	0		
GI: Week 2 (n=996, 1032)	0	3		
GI: Week 82 (n=834, 899)	2	1		
GI: Week 102 (n=49, 46)	0	0		
Musculoskeletal: Week 2 (n=1, 2)	1	0		
Musculoskeletal: Week 82 (n=834, 897)	11	7		
Musculoskeletal: Week 102 (n=41, 40)	1	0		
Neurological System: Week 2 (n=1, 2)	0	0		
Neurological System: Week 82 (n=834, 897)	1	2		
Neurological System: Week 102 (n=41, 40)	0	0		
Head,Eyes,Ears,Nose and Throat: Week 2 (n=1, 2)	1	0		
Head,Eyes,Ears,Nose and Throat:Week82 (n=834, 897)	5	3		
Head,Eyes,Ears,Nose and Throat:Week 102 (n=41, 40)	1	0		

Urogenital System: Week 2 (n=1, 2)	0	0		
Urogenital System: Week 82 (n=802, 866)	0	2		
Urogenital System: Week 102 (n=41, 39)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Time to First Occurrence of Major Adverse Cardiac Events (MACE)

End point title	Time to First Occurrence of Major Adverse Cardiac Events (MACE)[16]

End point description:

The cardiovascular adjudication committee was responsible for evaluation of MACE. Time to first event is the number of days between the subject's date of first dose of OKZ treatment either in the core or OLE study and the onset of the first event that is treatment-emergent under the OKZ treatment. Here, 9999 indicates median and confidence interval were not estimable. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study.

End point type	Primary

End point timeframe:

From the first dose of the study treatment up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1043	1061		
Units: days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Seroconversion

End point title	Time to Seroconversion[17]

End point description:

Blood samples were collected for the assessment of antidrug antibodies (ADA). Time to seroconversion was defined as (date of first positive confirmatory result minus date of negative result at baseline) plus one. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study.

End point type	Primary

End point timeframe:

Weeks 12, 28, 52, and 82 (EoT)

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	17		
Units: days				
median (full range (min-max))				
Week 12 (n=6, 7)	85.0 (76 to 85)	85.0 (83 to 96)		
Week 28 (n=4, 7)	197.0 (197 to 198)	198.0 (196 to 205)		
Week 52 (n=5, 3)	365.0 (365 to 366)	364.0 (361 to 367)		
Week 82 (n=2, 17)	568.5 (561 to 576)	575.0 (265 to 589)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with ADA and Positive Neutralizing Antibodies (NAb) to OKZ

End point title	Number of Subjects with ADA and Positive Neutralizing Antibodies (NAb) to OKZ[18]

End point description:

Blood samples were collected for assessment of ADA and NAb. The number of subjects with a positive result is relative to the number of subjects with a sample at each visit. The safety population included all subjects who received at least 1 dose of study treatment during the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Primary

End point timeframe:

OLE Baseline and Weeks 12, 28, 52 and 82 (EoT)

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	988	1015		
Units: subjects				
number (not applicable)				
ADA: Week 12 (988, 1015)	27	28		
ADA: Week 28 (943, 972)	30	26		
ADA: Week 52 (873, 916)	29	17		
ADA: Week 82 (825, 880)	24	35		
NAb: Week 12 (27, 28)	1	0		
NAb: Week 28 (30, 26)	3	0		
NAb: Week 52 (28, 17)	0	0		

NAb: Week 82 (24, 35)	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved American College of Rheumatology 20 (ACR20) Response Criteria

End point title	Percentage of Subjects who Achieved American College of Rheumatology 20 (ACR20) Response Criteria

End point description:

The ACR-20 was defined as an improvement of at least 20 % in at least 3 of the following 5 components of ACR core set: subject global assessment of disease activity, subject assessment of pain, health assessment questionnaire-disability index (HAQ-DI), physician global assessment, and level of acute phase reactant. Response was calculated relative to the core baseline, the last available assessment prior to the first dose of the study treatment in the core study. The modified Intent-to-Treat (mITT) population included all subjects who signed an informed consent form (ICF) for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study.

End point type	Secondary

End point timeframe:

At Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1057	1047		
Units: percentage of subjects				
number (not applicable)				
Week 12	81.5	82.4		
Week 20	80.4	81.3		
Week 28	79.4	79.2		
Week 40	75.2	75.9		
Week 52	73.8	74.8		
Week 64	73.5	73.9		
Week 82	76.7	79.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved American College of Rheumatology 50 (ACR50) Response Criteria

End point title	Percentage of Subjects who Achieved American College of Rheumatology 50 (ACR50) Response Criteria

End point description:

The ACR-50 was defined as an improvement of at least 50 % in at least 3 of the following 5 components of ACR core set: subject global assessment of disease activity, subject assessment of pain, HAQ-DI, physician global assessment, and level of acute phase reactant. Response was calculated relative to the core baseline, the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study.

End point type	Secondary

End point timeframe:

At Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1057	1047		
Units: percentage of subjects				
number (not applicable)				
Week 12	56.6	57.4		
Week 20	57.4	58.0		
Week 28	56.5	58.3		
Week 40	56.8	56.7		
Week 52	53.3	57.9		
Week 64	55.3	55.7		
Week 82	57.5	59.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved American College of Rheumatology 70 (ACR70) Response Criteria

End point title	Percentage of Subjects who Achieved American College of Rheumatology 70 (ACR70) Response Criteria

End point description:

The ACR-70 was defined as an improvement of at least 70 % in at least 3 of the following 5 components of ACR core set: subject global assessment of disease activity, subject assessment of pain, HAQ-DI, physician global assessment, and level of acute phase reactant. Response was calculated relative to the core baseline, the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study.

End point type	Secondary

End point timeframe:

At Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1057	1047		
Units: percentage of subjects				
number (not applicable)				
Week 12	31.2	34.6		
Week 20	33.9	33.7		
Week 28	34.7	34.1		
Week 40	35.5	35.2		
Week 52	35.0	37.0		
Week 64	35.3	37.0		
Week 82	36.1	37.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Simplified Disease Activity Index Remission (SDAI)

End point title	Percentage of Subjects with Simplified Disease Activity Index Remission (SDAI)

End point description:

The SDAI was calculated in the statistical database for analysis purposes using the swollen joint count (SJC [28 joints]), tender joint count (TJC [28 joints]), C-reactive protein (CRP) mg/deciliter (dL), the Patient Global Assessment of Disease Activity (Visual Analog Scale [VAS]) (in centimeter [cm]), and the Physician Global Assessment (VAS) (in centimeter [cm]) according to the following formula: SDAI = SJC + TJC + Patient Global Assessment of Disease Activity (VAS) + Physician Global Assessment (VAS) + CRP (mg/dL). The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study.

End point type	Secondary

End point timeframe:

At Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1057	1047		
Units: percentage of subjects				
number (not applicable)				
Week 12	15.1	18.3		
Week 20	18.2	18.8		
Week 28	18.6	18.9		
Week 40	19.3	20.2		
Week 52	20.9	21.7		
Week 64	21.0	24.6		
Week 82	21.9	25.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Disease Activity Score 28-Joint C-Reactive Protein (DAS28 [CRP]) < 3.2 Response Rate

End point title	Percentage of Subjects with Disease Activity Score 28-Joint C-Reactive Protein (DAS28 [CRP]) < 3.2 Response Rate

End point description:

The DAS28 (CRP) was calculated in the statistical database for analysis purposes using the SJC (28 joints), TJC (28 joints), CRP level, and the Patient Global Assessment of Disease Activity (VAS) (in millimeters [mm]) according to the following formula: DAS28 (CRP) = 0.56 × √(TJC) + 0.28 × √(SJC) + 0.36 × lognat (CRP + 1) + 0.014 × Patient Global Assessment of Disease activity (VAS) + 0.96. The 28 joints evaluated for the SJC and TJC were as follows: shoulders, elbows, wrists, interphalangeal (IP) on digit 1, proximal interphalangeal (PIP) on digits 2 to 5, metacarpophalangeal (MCP) on digits 1 to 5, and knees. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study.

End point type	Secondary

End point timeframe:

At Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1057	1047		
Units: percentage of subjects				
number (not applicable)				
Week 12	65.1	65.8		
Week 20	66.9	68.3		
Week 28	65.1	66.8		
Week 40	65.3	66.3		
Week 52	64.4	65.3		
Week 64	64.4	64.8		
Week 82	67.0	68.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline over Time in DAS28 (CRP) Scores

End point title	Change from Baseline over Time in DAS28 (CRP) Scores

End point description:

The DAS28 (CRP) was calculated in the statistical database for analysis purposes using the SJC (28 joints), TJC (28 joints), CRP level, and the Patient Global Assessment of Disease Activity (VAS) (in mm) according to the following formula: DAS28 (CRP) = 0.56 × √(TJC) + 0.28 × √(SJC) + 0.36 × lognat (CRP + 1) + 0.014 × Patient Global Assessment of Disease activity (VAS) + 0.96.
The 28 joints evaluated for the SJC and TJC were as follows: shoulders, elbows, wrists,IP on digit 1, PIP on digits 2 to 5, MCP on digits 1 to 5, and knees, where higher scores indicated greater disease activity. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	998	987		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=998, 987)	-3.035 (± 1.1372)	-3.123 (± 1.1884)		
Week 20 (n=983, 970)	-3.135 (± 1.1646)	-3.166 (± 1.1625)		
Week 28 (n=955, 949)	-3.157 (± 1.1540)	-3.196 (± 1.1608)		
Week 40 (n=927, 919)	-3.224 (± 1.1391)	-3.248 (± 1.1901)		
Week 52 (n=888, 890)	-3.282 (± 1.1132)	-3.338 (± 1.1726)		
Week 64 (n=874, 876)	-3.314 (± 1.0749)	-3.403 (± 1.1466)		
Week 82 (n=825, 841)	-3.218 (± 1.1703)	-3.263 (± 1.3142)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Measure of Physical Ability Based on HAQ-DI Scores

End point title	Change From Baseline in the Measure of Physical Ability Based on HAQ-DI Scores

End point description:

The HAQ-DI assessed the degree of difficulty experienced in 8 domains of daily living activities using 20 questions. The domains are dressing, grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities, each domain consists of 2 or 3 items. For each question, the level of difficulty is scored from 0 to 3 where 0: without any difficulty, 1: with some difficulty, 2: much difficulty, and 3: unable to do. Each category is given a score 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. Baseline was defined as the last available assessment prior to the 1st dose of the

study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64, and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1001	986		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 12 (n=1001, 986)	-0.67 (± 0.628)	-0.74 (± 0.648)		
Week 20 (n=982, 968)	-0.70 (± 0.631)	-0.74 (± 0.640)		
Week 28 (n=955, 947)	-0.71 (± 0.645)	-0.75 (± 0.652)		
Week 40 (n=926, 917)	-0.72 (± 0.663)	-0.75 (± 0.672)		
Week 52 (n=888, 888)	-0.72 (± 0.670)	-0.77 (± 0.671)		
Week 64 (n=876, 877)	-0.74 (± 0.643)	-0.77 (± 0.671)		
Week 82 (n=828, 855)	-0.72 (± 0.680)	-0.74 (± 0.695)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Improvement from Baseline in HAQ-DI Score >=0.22

End point title	Percentage of Subjects with Improvement from Baseline in HAQ-DI Score >=0.22

End point description:

The HAQ-DI assesses the degree of difficulty experienced in 8 domains of daily living activities using 20 questions. For each question, the level of difficulty is scored from 0 to 3 where 0 = without any difficulty, 1 = with some difficulty, 2 = much difficulty, and 3 = unable to do. The HAQ-DI was calculated by dividing the sum of the category scores by the number of categories with at least 1 question answered. Response was calculated relative to the core baseline, the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study.

End point type	Secondary

End point timeframe:

At Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1057	1047		
Units: percentage of subjects				
number (not applicable)				
Week 12	75.6	73.6		
Week 20	73.2	74.0		
Week 28	71.8	72.3		
Week 40	68.3	70.3		
Week 52	66.1	67.3		
Week 64	67.4	66.8		
Week 82 (EoT)	69.9	72.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form-36 (SF-36) Physical Component Summary Scores

End point title	Change From Baseline in Short Form-36 (SF-36) Physical Component Summary Scores

End point description:

The SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score, the less disability. An increase from baseline indicated improvement. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	988	973		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n=988, 973)	9.596 (9.0700 to 10.1212)	9.953 (9.4134 to 10.4929)		
Week 20 (n=941, 928)	9.809 (9.2926 to 10.3247)	10.025 (9.5020 to 10.5489)		
Week 28 (n=945, 934)	9.836 (9.2709 to 10.4008)	9.977 (9.4130 to 10.5417)		
Week 40 (n=921, 911)	10.294 (9.7051 to 10.8820)	10.214 (9.6452 to 10.7829)		

Week 52 (n=883, 882)	10.517 (9.9154 to 11.1184)	10.914 (10.3228 to 11.5051)		
Week 64 (n=871, 871)	10.741 (10.1367 to 11.3447)	10.877 (10.2724 to 11.4824)		
Week 82 (n=823, 852)	10.140 (9.5010 to 10.7784)	10.413 (9.7783 to 11.0474)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SF-36 Mental Component Summary Total Scores

End point title	Change From Baseline in SF-36 Mental Component Summary Total Scores

End point description:

The SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score, the less disability. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. An increase from baseline indicated improvement. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	988	973		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n=988, 973)	6.364 (5.7536 to 6.9746)	5.880 (5.2267 to 6.5331)		
Week 20 (n=941, 928)	6.614 (6.0045 to 7.2242)	5.953 (5.3257 to 6.5813)		
Week 28 (n=945, 934)	6.759 (6.0791 to 7.4381)	6.114 (5.4344 to 6.7928)		
Week 40 (n=921, 911)	6.912 (6.2419 to 7.5823)	5.818 (5.1070 to 6.5292)		
Week 52 (n=883, 882)	6.644 (5.9444 to 7.3436)	5.926 (5.1902 to 6.6626)		
Week 64 (n=871, 871)	6.775 (6.0775 to 7.4729)	5.811 (5.0829 to 6.5400)		
Week 82 (n=823, 852)	6.258 (5.5216 to 6.9950)	6.144 (5.4040 to 6.8838)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life-5 Dimensions (EQ-5D) Scores

End point title	Change From Baseline in European Quality of Life-5 Dimensions (EQ-5D) Scores

End point description:

The EQ-5D consisted of a questionnaire used to self-rate health status. The EQ-5D records the subject's perceptions of their own current overall health and can be used to monitor changes with time. The self-assessment questionnaire is a description of 5 dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The subject was asked to grade their own current level of function in each dimension into 1 of 5 degrees of disability (extreme, severe, moderate, slight, or none). The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study), Week 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	988	971		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n=988, 971)	23.4 (21.68 to 25.04)	24.7 (22.87 to 26.45)		
Week 20 (n=941, 925)	23.5 (21.86 to 25.14)	25.1 (23.41 to 26.82)		
Week 28 (n=945, 931)	23.7 (21.94 to 25.47)	25.6 (23.79 to 27.33)		
Week 40 (n=921, 909)	24.5 (22.72 to 26.31)	25.8 (23.99 to 27.61)		
Week 52 (n=883, 880)	25.1 (23.29 to 26.96)	27.0 (25.10 to 28.85)		
Week 64 (n=871, 869)	26.0 (24.17 to 27.84)	27.2 (25.30 to 29.10)		
Week 82 (n=823, 850)	25.0 (23.19 to 26.85)	26.7 (24.75 to 28.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity Survey-Rheumatoid Arthritis (WPS-RA) Scores

End point title	Change From Baseline in Work Productivity Survey-Rheumatoid Arthritis (WPS-RA) Scores

End point description:

The WPS-RA assessed work productivity within and outside the home during the previous month. It contains 9 questions addressing employment status, productivity, and daily activities. One item addressed current employment. Two items capture selfreported work absences due to RA, and absences to non-paid work. Additional items captured the extent to which RA has interfered with the subject's work productivity on a scale of 0 to 10 (higher scores indicated less productivity), the number of days in the last month outside help was hired because of RA, and the number of days in the last month family, social, or leisure activities were missed because of RA. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation, randomized and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	353		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n=350, 353)	-10.79 (-13.697 to -7.874)	-14.43 (-18.082 to -10.785)		
Week 20 (n=315, 322)	-10.08 (-13.053 to -7.106)	-13.98 (-17.831 to -10.135)		
Week 28 (n=330, 339)	-10.00 (-13.068 to -6.932)	-13.25 (-17.254 to -9.250)		
Week 40 (n=326, 337)	-8.67 (-11.907 to -5.424)	-14.07 (-17.864 to -10.266)		
Week 52 (n=309, 323)	-9.84 (-13.016 to -6.661)	-13.87 (-17.831 to -9.909)		
Week 64 (n=303, 321)	-9.98 (-13.412 to -6.538)	-14.50 (-18.301 to -10.702)		
Week 82 (n=277, 294)	-8.48 (-12.291 to -4.677)	-13.50 (-17.278 to -9.729)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT Fatigue) Scores

End point title	Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT Fatigue) Scores

End point description:

FACIT-Fatigue is a 13-item tool that measured an individual's level of fatigue during their usual daily activities during the most recent week. The level of fatigue was measured on a 4-point Likert scale ranging from "Not at all" (0) to "Very much" (4). The total Score was the sum of all individual item scores, ranging from 0 to 52, where higher score = lower level of fatigue and indicates better quality of life. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	987	970		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n= 987, 970)	9.9 (9.22 to 10.51)	10.0 (9.31 to 10.69)		
Week 20 (n= 940, 924)	10.0 (9.39 to 10.67)	10.0 (9.36 to 10.72)		
Week 28 (n= 944, 930)	10.1 (9.44 to 10.81)	10.1 (9.40 to 10.83)		
Week 40 (n= 920, 908)	10.8 (10.10 to 11.48)	10.0 (9.26 to 10.74)		
Week 52 (n= 882, 880)	10.5 (9.81 to 11.25)	10.4 (9.69 to 11.19)		
Week 64 (n= 870, 869)	10.7 (10.00 to 11.44)	10.4 (9.61 to 11.11)		
Week 82 (n= 822, 849)	10.2 (9.49 to 10.99)	10.4 (9.66 to 11.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SDAI Scores

End point title	Change From Baseline in SDAI Scores

End point description:

The SDAI was calculated in the statistical database for analysis purposes using the SJC (28 joints), TJC (28 joints), CRP (mg/dL), the Patient Global Assessment of Disease Activity (VAS) (in cm), and the Physician Global Assessment (VAS) (in cm) according to the following formula: SDAI = SJC + TJC + Patient Global Assessment of Disease Activity (VAS) + Physician Global Assessment (VAS) + CRP (mg/dL). Lower scores indicated less disease activity. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized and

received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	965	952		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n= 965, 952)	-30.77 (-31.539 to -29.999)	-31.12 (-31.953 to -30.286)		
Week 20 (n= 956, 943)	-31.28 (-32.083 to -30.478)	-31.77 (-32.604 to -30.944)		
Week 28 (n= 929, 921)	-31.76 (-32.542 to -30.973)	-31.86 (-32.701 to -31.012)		
Week 40 (n= 896, 890)	-32.27 (-33.070 to -31.474)	-32.32 (-33.187 to -31.447)		
Week 52 (n= 863, 865)	-32.73 (-33.535 to -31.934)	-33.13 (-33.986 to -32.281)		
Week 64 (n= 848, 851)	-33.07 (-33.879 to -32.265)	-33.41 (-34.261 to -32.557)		
Week 82 (n= 800, 818)	-31.91 (-32.800 to -31.027)	-32.01 (-33.012 to -31.007)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Disease Activity Index (CDAI) Scores

End point title	Change from Baseline in Clinical Disease Activity Index (CDAI) Scores

End point description:

The CDAI was calculated in the statistical database for analysis purposes using the SJC (28 joints), TJC (28 joints), the Patient Global Assessment of Disease Activity (VAS) (in cm), and the Physician Global Assessment (VAS) (in cm) according to the following formula: CDAI = SJC + TJC + Patient Global Assessment of Disease Activity (VAS) + Physician Global Assessment (VAS). CDAI score ranged 0-76; lower scores indicated lower disease activity. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed in each analysis set.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	967	953		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n= 967, 953)	-29.01 (-29.750 to -28.260)	-29.22 (-30.028 to -28.419)		
Week 20 (n= 956, 943)	-29.53 (-30.310 to -28.754)	-29.90 (-30.694 to -29.096)		
Week 28 (n= 929, 922)	-29.99 (-30.748 to -29.227)	-30.01 (-30.824 to -29.197)		
Week 40 (n= 897, 891)	-30.52 (-31.285 to -29.748)	-30.45 (-31.291 to -29.613)		
Week 52 (n= 865, 865)	-30.99 (-31.759 to -30.217)	-31.26 (-32.080 to -30.434)		
Week 64 (n= 851, 853)	-31.31 (-32.090 to -30.534)	-31.51 (-32.326 to -30.686)		
Week 82 (n= 804, 829)	-30.17 (-31.032 to -29.305)	-30.23 (-31.193 to -29.276)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Moderate to Good Responses for European League Against Rheumatism (EULAR)

End point title	Percentage of Subjects with Moderate to Good Responses for European League Against Rheumatism (EULAR)

End point description:

A EULAR response was defined as either a moderate or a good response based on DAS28 (CRP). A moderate response was defined as either 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 >1.2. Good EULAR response was defined as DAS28 (CRP) <=3.2 with an improvement from Baseline >1.2. Response was calculated relative to the core baseline, the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study.

End point type	Secondary

End point timeframe:

Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1057	1047		
Units: percentage of subjects				
number (not applicable)				
Week 12	91.2	91.8		
Week 20	90.5	90.5		
Week 28	88.3	88.5		
Week 40	85.6	86.0		
Week 52	82.3	83.3		
Week 64	81.2	82.5		
Week 82	88.1	89.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ACR Response Criteria: TJC Score

End point title	Change from Baseline in ACR Response Criteria: TJC Score

End point description:

The TJC scores ranged from 0 – 68 (lower scores indicated less disease activity), where a decrease from baseline indicated improvement. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1014	1010		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n= 1014, 1010)	-17.49 (-18.177 to -16.812)	-18.24 (-18.994 to -17.490)		
Week 20 (n= 996, 993)	-18.10 (-18.816 to -17.393)	-18.67 (-19.412 to -17.937)		
Week 28 (n= 967, 972)	-18.17 (-18.867 to -17.465)	-18.81 (-19.598 to -18.025)		

Week 40 (n= 940, 940)	-18.46 (-19.169 to -17.751)	-19.23 (-20.037 to -18.418)		
Week 52 (n= 903, 911)	-18.86 (-19.606 to -18.111)	-19.73 (-20.516 to -18.937)		
Week 64 (n= 890, 898)	-19.06 (-19.793 to -18.335)	-19.99 (-20.798 to -19.179)		
Week 82 (n= 843, 876)	-18.25 (-19.023 to -17.474)	-18.84 (-19.690 to -17.982)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ACR Response Criteria: SJC Score

End point title	Change from Baseline in ACR Response Criteria: SJC Score

End point description:

The SJC score ranged between 0 – 66 (where higher score indicates more severity), with a decrease from baseline indicated improvement. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1014	1010		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n= 1014, 1010)	-12.60 (-13.094 to -12.107)	-12.83 (-13.325 to -12.344)		
Week 20 (n= 996, 993)	-12.79 (-13.262 to -12.316)	-13.02 (-13.522 to -12.517)		
Week 28 (n= 967, 972)	-12.99 (-13.451 to -12.528)	-13.02 (-13.537 to -12.508)		
Week 40 (n= 940, 940)	-13.18 (-13.662 to -12.707)	-13.28 (-13.787 to -12.772)		
Week 52 (n= 903, 911)	-13.34 (-13.842 to -12.834)	-13.50 (-14.009 to -12.985)		
Week 64 (n= 890, 898)	-13.37 (-13.894 to -12.848)	-13.54 (-14.062 to -13.026)		

Week 82 (n= 843, 876)	-12.84 (-13.369 to -12.306)	-12.96 (-13.540 to -12.389)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ACR Response Criteria: Subject's Global Assessment of Disease Activity (VAS) Score

End point title	Change from Baseline in ACR Response Criteria: Subject's Global Assessment of Disease Activity (VAS) Score

End point description:

Subject's Global Assessment of Disease Activity (VAS) score ranged from: 0 - 100, where 0 is "Very Well" and 100 is "Very Poorly", where higher score indicated worse outcomes. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1002	988		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n= 1002, 988)	-35.4 (-37.08 to -33.73)	-36.0 (-37.71 to -34.32)		
Week 20 (n= 983, 970)	-35.8 (-37.53 to -34.08)	-35.8 (-37.62 to -34.08)		
Week 28 (n= 956, 949)	-37.0 (-38.78 to -35.31)	-36.5 (-38.20 to -34.76)		
Week 40 (n= 927, 919)	-36.8 (-38.57 to -35.01)	-36.7 (-38.58 to -34.89)		
Week 52 (n= 889, 890)	-37.2 (-39.04 to -35.42)	-37.8 (-39.71 to -35.96)		
Week 64 (n= 877, 879)	-38.0 (-39.81 to -36.21)	-38.2 (-40.07 to -36.33)		
Week 82 (n= 829, 857)	-36.4 (-38.38 to -34.46)	-36.2 (-38.19 to -34.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ACR Response Criteria: Subject's Assessment of Pain (VAS) Score

End point title	Change From Baseline in ACR Response Criteria: Subject's Assessment of Pain (VAS) Score

End point description:

Subject's Assessment of Pain (VAS) score ranged from: 0 - 100, where 0 is "no pain" and 100 is "severe pain"; higher score indicated worse outcomes. Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1002	988		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n= 1002, 988)	-36.3 (-38.01 to -34.59)	-38.7 (-40.39 to -36.93)		
Week 20 (n= 983, 970)	-36.9 (-38.63 to -35.17)	-38.5 (-40.21 to -36.69)		
Week 28 (n= 956, 949)	-37.7 (-39.53 to -35.96)	-38.8 (-40.58 to -37.05)		
Week 40 (n= 927, 919)	-38.3 (-40.12 to -36.44)	-39.2 (-41.05 to -37.39)		
Week 52 (n= 889, 890)	-38.2 (-40.07 to -36.40)	-40.7 (-42.59 to -38.77)		
Week 64 (n= 877, 879)	-39.0 (-40.79 to -37.11)	-40.3 (-42.16 to -38.36)		
Week 82 (n= 829, 857)	-38.0 (-39.92 to -35.98)	-39.1 (-41.05 to -37.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ACR Response Criteria: Physician's Global Assessment (VAS) Score

End point title	Change From Baseline in ACR Response Criteria: Physician's Global Assessment (VAS) Score

End point description:

Physician's Global Assessment (VAS) score ranged from: 0 – 100, where 0 is "no disease activity" and 100 is "maximal disease activity" (higher score indicated worse outcomes) .Baseline was defined as the last available assessment prior to the first dose of the study treatment in the core study. The mITT population included all subjects who signed an ICF for participation in the OLE study, were randomized in the OLE study, and received at least 1 dose of study treatment in the OLE study. Here, n= number of subjects analysed at specific timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of the core study) and Weeks 12, 20, 28, 40, 52, 64 and 82 (EoT)

End point values	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	968	956		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 12 (n= 968, 956)	-48.9 (-50.21 to -47.53)	-50.3 (-51.68 to -49.00)		
Week 20 (n= 957, 946)	-49.8 (-51.17 to -48.46)	-51.8 (-53.14 to -50.43)		
Week 28 (n= 931, 925)	-50.5 (-51.84 to -49.14)	-51.0 (-52.37 to -49.59)		
Week 40 (n= 898, 893)	-51.9 (-53.24 to -50.57)	-51.8 (-53.23 to -50.38)		
Week 52 (n= 866, 867)	-52.7 (-54.04 to -51.35)	-53.8 (-55.11 to -52.41)		
Week 64 (n= 852, 855)	-53.4 (-54.70 to -52.00)	-53.7 (-55.11 to -52.26)		
Week 82 (n= 806, 832)	-52.0 (-53.58 to -50.52)	-52.0 (-53.59 to -50.42)		

Statistical analyses

No statistical analyses for this end point

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 up to 22 weeks after the last dose of the study treatment, approximately 102 weeks

Adverse event reporting additional description:

The safety population included all subjects who received OKZ q2w or q4w in OLE study, irrespective to treatment received in core studies. A TEAE was defined as an adverse event that first occurred or worsened in severity after the first dose of the OLE study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	OKZ 64 mg q4w (OLE)

Reporting group description:

OKZ 64 mg q4w (OLE) group includes all subjects who received OKZ 64 mg q4w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q4w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the EoT Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Reporting group title	OKZ 64 mg q2w (OLE)

Reporting group description:

OKZ 64 mg q2w (OLE) group includes all subjects who received OKZ 64 mg q2w in this study, irrespective to treatment in core study. Subjects who had received OKZ 64 q2w in the core study in which they had participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) received the same OKZ treatment regimen in the OLE study. Subjects who had received placebo (Study CL04041023 and CL04041022) or adalimumab (Study CL04041022) in the core study in which they had participated were randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study. The last dose of OKZ was administered at Week 80. After the EoT Visit (Week 82), subjects were scheduled for 3 Safety Follow-Up Visits up to Week 102.

Serious adverse events	OKZ 64 mg q4w (OLE)	OKZ 64 mg q2w (OLE)	
Total subjects affected by serious adverse events			
subjects affected / exposed	129 / 1043 (12.37%)	120 / 1061 (11.31%)	
number of deaths (all causes)	13	13	
number of deaths resulting from adverse events	13	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of thyroid gland			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system neoplasm			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cervix carcinoma stage II			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extranodal marginal zone B-cell lymphoma (MALT type)			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage III			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Marginal zone lymphoma			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma benign			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Salivary gland cancer			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion threatened			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sudden death			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lithiasis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Vascular stent occlusion			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	2 / 1043 (0.19%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermenstrual bleeding			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 1043 (0.19%)	4 / 1061 (0.38%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Asthmatic crisis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 1043 (0.67%)	5 / 1061 (0.47%)	
occurrences causally related to treatment / all	5 / 7	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			

subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 1043 (0.00%)	2 / 1061 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 1043 (0.19%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 1043 (0.00%)	2 / 1061 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			

subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haematoma			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Wrist fracture			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 1043 (0.29%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 1043 (0.00%)	2 / 1061 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachyarrhythmia			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	4 / 1043 (0.38%)	2 / 1061 (0.19%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 1043 (0.00%)	2 / 1061 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 1043 (0.19%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery aneurysm			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pineal gland cyst			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic cyst			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular myasthenia			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 1043 (0.10%)	2 / 1061 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 1043 (0.00%)	2 / 1061 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia obstructive			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis chronic			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland calculus			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 1043 (0.19%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperplastic cholecystopathy			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis contact			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			

subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	6 / 1043 (0.58%)	6 / 1061 (0.57%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint ankylosis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle contracture			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	7 / 1043 (0.67%)	7 / 1061 (0.66%)	
occurrences causally related to treatment / all	2 / 7	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	7 / 1043 (0.67%)	4 / 1061 (0.38%)	
occurrences causally related to treatment / all	3 / 7	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	5 / 1043 (0.48%)	4 / 1061 (0.38%)	
occurrences causally related to treatment / all	2 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	1 / 1043 (0.10%)	3 / 1061 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 1043 (0.19%)	2 / 1061 (0.19%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 1043 (0.19%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 1043 (0.19%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 1043 (0.00%)	3 / 1061 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Abscess limb			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 1043 (0.10%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			

subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess soft tissue			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bartholinitis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bullous erysipelas			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cat scratch disease			

subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalomyelitis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Latent tuberculosis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ludwig angina			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site abscess			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising soft tissue infection			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			

subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal abscess			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Streptococcal sepsis			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection pseudomonas			
subjects affected / exposed	1 / 1043 (0.10%)	0 / 1061 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 1043 (0.00%)	1 / 1061 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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 (OLE)	OKZ 64 mg q2w (OLE)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	418 / 1043 (40.08%)	454 / 1061 (42.79%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	95 / 1043 (9.11%)	115 / 1061 (10.84%)	
occurrences (all)	163	200	
Aspartate aminotransferase increased			
subjects affected / exposed	52 / 1043 (4.99%)	63 / 1061 (5.94%)	
occurrences (all)	80	94	
Vascular disorders			

Hypertension			
subjects affected / exposed	32 / 1043 (3.07%)	44 / 1061 (4.15%)	
occurrences (all)	33	49	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	46 / 1043 (4.41%)	60 / 1061 (5.66%)	
occurrences (all)	66	95	
Neutropenia			
subjects affected / exposed	42 / 1043 (4.03%)	57 / 1061 (5.37%)	
occurrences (all)	79	92	
Lymphopenia			
subjects affected / exposed	41 / 1043 (3.93%)	50 / 1061 (4.71%)	
occurrences (all)	62	90	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	71 / 1043 (6.81%)	87 / 1061 (8.20%)	
occurrences (all)	90	108	
Upper respiratory tract infection			
subjects affected / exposed	59 / 1043 (5.66%)	67 / 1061 (6.31%)	
occurrences (all)	70	84	
Bronchitis			
subjects affected / exposed	59 / 1043 (5.66%)	45 / 1061 (4.24%)	
occurrences (all)	66	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2016	Significant changes to the protocol included: • Inclusion criterion and exclusion added. • Additional guidance for monitoring and reporting hepatotoxicity events was added. Potential hepatotoxicity events that fulfilled any of the following criteria were to be recorded as SAEs: ALT >3 × ULN and total bilirubin >2 × ULN; ALT >8 × ULN at any time, regardless of total bilirubin or accompanying symptoms; ALT >5 × ULN for ≥2 weeks, regardless of total bilirubin or accompanying symptoms; ALT >3 × ULN, accompanied by symptoms consistent with hepatic injury. • Additional guidance for the management of latent tuberculosis infection was added. • The definition of moderate response in the efficacy endpoint assessing percentage 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.
06 March 2019	Significant changes to the protocol included: • Addition of a sterile, preservative-free, single-use solution for injection presented in a prefilled syringe, in addition to the 2 milliliter glass vials already available, for presentation of OKZ. Details regarding distribution, preparation, administration, and return of used and unused study treatment were revised to account for the prefilled syringe. • Malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin) was added to the list of permanent discontinuation of study treatment criteria, and suspected malignancy was added to the list of temporary discontinuation of study treatment criteria. • Sponsor name was modified from R-Pharm to R-Pharm International, LLC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported