



Clinical trial results:

A Phase IIb Multicenter, Randomized, Double-blind, Placebo-Controlled Dose-Range Finding Study of ALX-0061 Administered Subcutaneously in Combination with Methotrexate, in Subjects with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy

Summary

EudraCT number	2014-003033-26
Trial protocol	BE HU CZ DE ES BG
Global end of trial date	08 August 2016

Results information

Result version number	v1 (current)
This version publication date	10 August 2017
First version publication date	10 August 2017

Trial information

Trial identification

Sponsor protocol code	ALX0061-C201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02309359
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ablynx
Sponsor organisation address	Technologiepark 21, Zwijnaarde, Belgium, 9052
Public contact	Medical Monitor, Ablynx, +32 92620000, clinicaltrials@ablynx.com
Scientific contact	Medical Monitor, Ablynx, +32 92620000, clinicaltrials@ablynx.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2016
Global end of trial reached?	Yes
Global end of trial date	08 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of dose regimens of ALX-0061 compared to placebo administered subcutaneously (s.c.) in combination with Methotrexate (MTX) to subjects with active rheumatoid arthritis (RA) despite MTX therapy.

Subjects who completed the 24-week assessment period and achieved at least 20% improvement in swollen joint count (SJC) and/or tender joint count (TJC) at Week 24 of study ALX0061-C201 were invited to participate in an open-label extension (OLE) study ALX0061-C203 (if the study was approved in their country and selection criteria were met).

Protection of trial subjects:

Only subjects who met all the study inclusion criteria and none of the exclusion criteria were to be randomized to study treatment. All subjects were free to withdraw from the clinical study at any time for any reason. Close monitoring of all subjects was to be adhered to throughout the study.

Background therapy:

Minimum treatment duration with MTX of 4 months prior to screening and stable dose and route of administration of MTX (12.5-25.0 mg weekly) maintained during the 6 consecutive weeks before screening and for the duration of the study. Commercially available MTX (not provided by the Sponsor) was used in this study.

Evidence for comparator: -

Actual start date of recruitment	30 January 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	27 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Georgia: 41
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 15
Country: Number of subjects enrolled	Moldova, Republic of: 7
Country: Number of subjects enrolled	Serbia: 24
Country: Number of subjects enrolled	Mexico: 59
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Poland: 93
Country: Number of subjects enrolled	Romania: 3

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bulgaria: 26
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Hungary: 29
Worldwide total number of subjects	345
EEA total number of subjects	172

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)	285
From 65 to 84 years	60
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 345 subjects were recruited at 63 sites located in Europe (46 sites; 259 subjects), Latin America (7 sites; 59 subjects) and North America (10 sites; 27 subjects). Consent was obtained from the first subject on 30 Jan 2015; the last subject completed the final visit on 8 Aug 2016.

Pre-assignment

Screening details:

Of the 712 subjects screened, 367 were screen failures and 345 were randomly assigned to treatment (Intent-to-treat population). All subjects enrolled received study drug and were included in the safety population. All subjects who received at least one dose of ALX-0061 (i.e., 276 subjects) were included in the pharmacokinetic (PK) population.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ALX-0061 75 mg q4w + MTX

Arm description:

ALX-0061 75 mg every 4 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.

Arm type	Experimental
Investigational medicinal product name	vobarilizumab
Investigational medicinal product code	ALX-0061
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage of 75 mg every 4 weeks administered via a subcutaneous injection in the abdominal region.

Investigational medicinal product name	Placebo
Investigational medicinal product code	ALX-0061 Placebo
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo every 2 weeks administered via a subcutaneous injection in the abdominal region.

Arm title	ALX-0061 150 mg q4w + MTX
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Arm description:

ALX-0061 150 mg every 4 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.

Arm type	Experimental
Investigational medicinal product name	vobarilizumab
Investigational medicinal product code	ALX-0061
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:	
Dosage of 150 mg every 4 weeks administered via a subcutaneous injection in the abdominal region.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	ALX-0061 Placebo
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Placebo every 2 weeks administered via a subcutaneous injection in the abdominal region.	
Arm title	ALX-0061 150 mg q2w + MTX
Arm description:	
ALX-0061 150 mg every 2 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Arm type	Experimental
Investigational medicinal product name	vobarilizumab
Investigational medicinal product code	ALX-0061
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Dosage of 150 mg every 2 weeks administered via a subcutaneous injection in the abdominal region.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	ALX-0061 Placebo
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Placebo every 2 weeks administered via a subcutaneous injection in the abdominal region.	
Arm title	ALX-0061 225 mg q2w + MTX
Arm description:	
ALX-0061 225 mg every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Arm type	Experimental
Investigational medicinal product name	vobarilizumab
Investigational medicinal product code	ALX-0061
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Dosage of 225 mg every 2 weeks administered via a subcutaneous injection in the abdominal region.	
Arm title	Placebo q2w + MTX
Arm description:	
placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Placebo every 2 weeks administered via a subcutaneous injection in the abdominal region.	

Number of subjects in period 1	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX
Started	69	70	68
Completed	57	62	57
Not completed	12	8	11
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	2	2	4
Adverse event, non-fatal	4	5	5
Other	2	-	2
Lost to follow-up	-	-	-
Lack of efficacy	3	1	-

Number of subjects in period 1	ALX-0061 225 mg q2w + MTX	Placebo q2w + MTX
Started	69	69
Completed	57	60
Not completed	12	9
Adverse event, serious fatal	-	-
Consent withdrawn by subject	4	-
Adverse event, non-fatal	4	4
Other	3	2
Lost to follow-up	1	-
Lack of efficacy	-	3

Baseline characteristics

Reporting groups

Reporting group title	ALX-0061 75 mg q4w + MTX
Reporting group description: ALX-0061 75 mg every 4 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Reporting group title	ALX-0061 150 mg q4w + MTX
Reporting group description: ALX-0061 150 mg every 4 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Reporting group title	ALX-0061 150 mg q2w + MTX
Reporting group description: ALX-0061 150 mg every 2 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Reporting group title	ALX-0061 225 mg q2w + MTX
Reporting group description: ALX-0061 225 mg every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Reporting group title	Placebo q2w + MTX
Reporting group description: placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	

Reporting group values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX
Number of subjects	69	70	68
Age categorical Units: Subjects			
Adults (18-64 years)	59	59	56
From 65-84 years	10	11	12
Age continuous Units: years			
arithmetic mean	53.3	52	51.9
standard deviation	± 10.35	± 13.16	± 11.93
Gender categorical Units: Subjects			
Female	58	62	59
Male	11	8	9

Reporting group values	ALX-0061 225 mg q2w + MTX	Placebo q2w + MTX	Total
Number of subjects	69	69	345
Age categorical Units: Subjects			
Adults (18-64 years)	55	56	285
From 65-84 years	14	13	60
Age continuous Units: years			
arithmetic mean	52.3	52.8	-
standard deviation	± 13.36	± 11.92	-

Gender categorical Units: Subjects			
Female	55	55	289
Male	14	14	56

Subject analysis sets

Subject analysis set title	ALX-0061 total
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects randomized to the ALX0061 75 mg q4w, ALX-0061 150 q4w, ALX-0061 150 mg q2w and ALX-0061 225 mg q2w groups

Reporting group values	ALX-0061 total		
Number of subjects	276		
Age categorical Units: Subjects			
Adults (18-64 years)	229		
From 65-84 years	47		
Age continuous Units: years			
arithmetic mean	52.4		
standard deviation	± 12.21		
Gender categorical Units: Subjects			
Female	234		
Male	42		

End points

End points reporting groups

Reporting group title	ALX-0061 75 mg q4w + MTX
Reporting group description: ALX-0061 75 mg every 4 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Reporting group title	ALX-0061 150 mg q4w + MTX
Reporting group description: ALX-0061 150 mg every 4 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Reporting group title	ALX-0061 150 mg q2w + MTX
Reporting group description: ALX-0061 150 mg every 2 weeks + placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Reporting group title	ALX-0061 225 mg q2w + MTX
Reporting group description: ALX-0061 225 mg every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Reporting group title	Placebo q2w + MTX
Reporting group description: placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24. The last study drug administration was at the Week 22 visit.	
Subject analysis set title	ALX-0061 total
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects randomized to the ALX0061 75 mg q4w, ALX-0061 150 q4w, ALX-0061 150 mg q2w and ALX-0061 225 mg q2w groups	

Primary: Proportion of subjects achieving American College of Rheumatology (ACR) 20 response at Week 12

End point title	Proportion of subjects achieving American College of Rheumatology (ACR) 20 response at Week 12
End point description: The primary endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing ACR20 response at Week 12 were treated as non responders.	
End point type	Primary
End point timeframe: at Week 12 visit	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[1]	70 ^[2]	68 ^[3]	69 ^[4]
Units: percent responders	75	81	78	72

Notes:

[1] - Intent-to-treat population

[2] - Intent-to-treat population

[3] - Intent-to-treat population

[4] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[5]			
Units: percent responders	62			

Notes:

[5] - Intent-to-treat population

Statistical analyses

Statistical analysis title	Cochran Armitage Test for Trend
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Statistical analysis description:

Under the assumption of monotonicity, a Cochran-Armitage trend test was performed as the primary efficacy analysis. Data were analyzed according to the ITT principle; thus, subjects were analyzed according to the treatment to which they were assigned. Subjects with missing ACR20 response at Week 12 were treated as non responders (non responder imputation approach).

Comparison groups	ALX-0061 75 mg q4w + MTX v ALX-0061 150 mg q4w + MTX v ALX-0061 150 mg q2w + MTX v ALX-0061 225 mg q2w + MTX v Placebo q2w + MTX
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.172
Method	Cochran-Armitage trend test

Notes:

[6] - The null hypothesis of this test was that there is no difference in the percentage of subjects achieving ACR20 response between the treatment groups and the alternative hypothesis was that the percentage of subjects achieving ACR20 response increases with increasing dose level.

Secondary: Proportion of subjects with ACR20 response at Week 24

End point title	Proportion of subjects with ACR20 response at Week 24
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End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 24 were treated as non responders.

End point type	Secondary
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End point timeframe:

at Week 24 visit

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[7]	70 ^[8]	68 ^[9]	69 ^[10]
Units: percent responders	74	79	72	75

Notes:

[7] - Intent-to-treat population

[8] - Intent-to-treat population

[9] - Intent-to-treat population

[10] - Intent-to-treat population

End point values	Placebo q2w + MTX			
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Subject group type	Reporting group			
Number of subjects analysed	69 ^[11]			
Units: percent responders	74			

Notes:

[11] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with ACR50 response at Weeks 12 and 24

End point title	Proportion of subjects with ACR50 response at Weeks 12 and 24
End point description: This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.	
End point type	Secondary
End point timeframe: at Week 12 and Week 24 visits	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[12]	70 ^[13]	68 ^[14]	69 ^[15]
Units: percent responders				
Week 12	29	44	41	45
Week 24	48	56	54	61

Notes:

[12] - Intent-to-treat population

[13] - Intent-to-treat population

[14] - Intent-to-treat population

[15] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[16]			
Units: percent responders				
Week 12	28			
Week 24	39			

Notes:

[16] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with ACR70 response at Weeks 12 and 24

End point title	Proportion of subjects with ACR70 response at Weeks 12 and 24
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End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.

End point type Secondary

End point timeframe:

at Week 12 and Week 24 visit

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[17]	70 ^[18]	68 ^[19]	69 ^[20]
Units: percent responders				
Week 12	14	21	19	17
Week 24	23	33	22	45

Notes:

[17] - Intent-to-treat population

[18] - Intent-to-treat population

[19] - Intent-to-treat population

[20] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[21]			
Units: percent responders				
Week 12	9			
Week 24	17			

Notes:

[21] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with Low Disease Activity (LDA) using Disease Activity Score 28 (DAS28) using C-reactive protein (CRP)

End point title Proportion of subjects with Low Disease Activity (LDA) using Disease Activity Score 28 (DAS28) using C-reactive protein (CRP)

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.

End point type Secondary

End point timeframe:

at Week 12 and Week 24 visits

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[22]	70 ^[23]	68 ^[24]	69 ^[25]
Units: percent				
Week 12	23	53	47	58
Week 24	38	57	60	70

Notes:

[22] - Intent-to-treat population

[23] - Intent-to-treat population

[24] - Intent-to-treat population

[25] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[26]			
Units: percent				
Week 12	23			
Week 24	29			

Notes:

[26] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with LDA using DAS28 using Erythrocyte Sedimentation Rate (ESR)

End point title	Proportion of subjects with LDA using DAS28 using Erythrocyte Sedimentation Rate (ESR)
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End point description:

Subjects with low disease activity includes subjects who are in remission. This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.

End point type	Secondary
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End point timeframe:

at Week 12 and Week 24 visits

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[27]	70 ^[28]	68 ^[29]	69 ^[30]
Units: percent				
Week 12	19	51	43	48
Week 24	35	54	49	67

Notes:

[27] - Intent-to-treat population

[28] - Intent-to-treat population

[29] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[31]			
Units: percent				
Week 12	16			
Week 24	19			

Notes:

[31] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with LDA using Simplified Disease Activity Index (SDAI)

End point title	Proportion of subjects with LDA using Simplified Disease Activity Index (SDAI)
End point description: Subjects with low disease activity includes subjects who are in remission. This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.	
End point type	Secondary
End point timeframe: at Week 12 and Week 24 visits	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[32]	70 ^[33]	68 ^[34]	69 ^[35]
Units: percent				
Week 12	28	49	43	36
Week 24	42	49	51	67

Notes:

[32] - Intent-to-treat population

[33] - Intent-to-treat population

[34] - Intent-to-treat population

[35] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[36]			
Units: percent				
Week 12	25			
Week 24	32			

Notes:

[36] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with LDA using Clinical Disease Activity Index (CDAI)

End point title	Proportion of subjects with LDA using Clinical Disease Activity Index (CDAI)
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End point description:

Subjects with low disease activity includes subjects who are in remission. This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.

End point type	Secondary
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End point timeframe:

at Week 12 and Week 24 visits

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[37]	70 ^[38]	68 ^[39]	69 ^[40]
Units: percent				
Week 12	32	44	38	33
Week 24	42	47	43	62

Notes:

[37] - Intent-to-treat population

[38] - Intent-to-treat population

[39] - Intent-to-treat population

[40] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[41]			
Units: percent				
Week 12	25			
Week 24	33			

Notes:

[41] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with European League Against Rheumatism

(EULAR) (CRP) good response

End point title	Proportion of subjects with European League Against Rheumatism (EULAR) (CRP) good response
End point description: This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.	
End point type	Secondary
End point timeframe: at Week 12 and Week 24 visits	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[42]	70 ^[43]	68 ^[44]	69 ^[45]
Units: percent				
Week 12	22	51	44	57
Week 24	38	56	57	68

Notes:

[42] - Intent-to-treat population

[43] - Intent-to-treat population

[44] - Intent-to-treat population

[45] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[46]			
Units: percent				
Week 12	22			
Week 24	28			

Notes:

[46] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in remission using DAS28 (ESR)

End point title	Proportion of subjects in remission using DAS28 (ESR)
End point description: This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.	
End point type	Secondary
End point timeframe: at Week 12 and Week 24 visits	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[47]	70 ^[48]	68 ^[49]	69 ^[50]
Units: percent				
Week 12	4	37	22	30
Week 24	25	37	34	54

Notes:

[47] - Intent-to-treat population

[48] - Intent-to-treat population

[49] - Intent-to-treat population

[50] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[51]			
Units: percent				
Week 12	9			
Week 24	12			

Notes:

[51] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in remission using SDAI

End point title	Proportion of subjects in remission using SDAI
End point description:	
This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.	
End point type	Secondary
End point timeframe:	
at Week 12 and Week 24 visits	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[52]	70 ^[53]	68 ^[54]	69 ^[55]
Units: percent				
Week 12	3	11	9	7
Week 24	10	19	15	20

Notes:

[52] - Intent-to-treat population

[53] - Intent-to-treat population

[54] - Intent-to-treat population

[55] - Intent-to-treat population

End point values	Placebo q2w +			
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	MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[56]			
Units: percent				
Week 12	4			
Week 24	9			

Notes:

[56] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in remission using CDAI

End point title	Proportion of subjects in remission using CDAI
End point description:	
This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.	
End point type	Secondary
End point timeframe:	
at Week 12 and Week 24 visits	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[57]	70 ^[58]	68 ^[59]	69 ^[60]
Units: percent				
Week 12	4	10	6	7
Week 24	14	19	12	19

Notes:

[57] - Intent-to-treat population

[58] - Intent-to-treat population

[59] - Intent-to-treat population

[60] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[61]			
Units: percent				
Week 12	4			
Week 24	10			

Notes:

[61] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in remission using Boolean defined remission criteria

End point title	Proportion of subjects in remission using Boolean defined remission criteria
End point description: This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at the concerned visit were treated as non responders.	
End point type	Secondary
End point timeframe: at Week 12 and Week 24 visits	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[62]	70 ^[63]	68 ^[64]	69 ^[65]
Units: percent				
Week 12	0	7	3	6
Week 24	9	13	9	19

Notes:

[62] - Intent-to-treat population

[63] - Intent-to-treat population

[64] - Intent-to-treat population

[65] - Intent-to-treat population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[66]			
Units: percent				
Week 12	4			
Week 24	9			

Notes:

[66] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI)

End point title	Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI)
End point description: Missing values were imputed with the last non-missing observation (i.e., LOCF imputation).	
End point type	Secondary
End point timeframe: From baseline till Week 24	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[67]	68 ^[68]	64 ^[69]	67 ^[70]
Units: not applicable				
arithmetic mean (standard error)				
Week 12	-0.696 (± 0.0857)	-0.619 (± 0.0657)	-0.771 (± 0.0763)	-0.615 (± 0.0858)
Week 24	-0.82 (± 0.0913)	-0.665 (± 0.0682)	-0.876 (± 0.0802)	-0.772 (± 0.0926)

Notes:

[67] - Intent-to-treat population, number of subjects with data available

[68] - Intent-to-treat population, number of subjects with data available

[69] - Intent-to-treat population, number of subjects with data available

[70] - Intent-to-treat population, number of subjects with data available

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	67 ^[71]			
Units: not applicable				
arithmetic mean (standard error)				
Week 12	-0.613 (± 0.0718)			
Week 24	-0.662 (± 0.0798)			

Notes:

[71] - Intent-to-treat population, number of subjects with data available

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in physical component score of Short Form Health Survey (SF-36)

End point title	Change from baseline in physical component score of Short Form Health Survey (SF-36)
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End point description:

End point type	Secondary
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End point timeframe:

from baseline till Week 24

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61 ^[72]	66 ^[73]	58 ^[74]	60 ^[75]
Units: not applicable				
arithmetic mean (standard error)				
Week 12	7.372 (± 0.9136)	7.1 (± 0.7477)	6.534 (± 0.8878)	7.778 (± 0.994)
Week 24	10.412 (± 1.0642)	8.725 (± 0.9194)	8.835 (± 1.009)	10.762 (± 1.1497)

Notes:

[72] - Intent-to-treat population, number of subjects with data available (N=61 at Week 12; N=58 at Week24)

[73] - Intent-to-treat population, number of subjects with data available (N=66 at Week 12; N=62 at Week24)

[74] - Intent-to-treat population, number of subjects with data available (N=58 at Weeks 12 and 24)

[75] - Intent-to-treat population, number of subjects with data available (N=60 at Week 12; N=58 at Week24)

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	59 ^[76]			
Units: not applicable				
arithmetic mean (standard error)				
Week 12	5.413 (± 0.7813)			
Week 24	7.255 (± 0.9483)			

Notes:

[76] - Intent-to-treat population, number of subjects with data available (N=59 at Weeks 12 and 24)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mental component score of Short Form Health Survey (SF-36)

End point title	Change from baseline in mental component score of Short Form Health Survey (SF-36)
End point description:	
End point type	Secondary
End point timeframe:	
from Baseline till Week 24	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61 ^[77]	66 ^[78]	58 ^[79]	60 ^[80]
Units: not applicable				
arithmetic mean (standard error)				

Week 12	9.096 (± 1.4966)	7.249 (± 1.1237)	9.749 (± 1.4177)	5.686 (± 1.6485)
Week 24	9.857 (± 1.5326)	7.962 (± 1.3932)	11.739 (± 1.4159)	8.981 (± 1.6876)

Notes:

[77] - Intent-to-treat population, number of subjects with data available (N=61 at Week 12; N=58 at Week24)

[78] - Intent-to-treat population, number of subjects with data available (N=66 at Week 12; N=62 at Week24)

[79] - Intent-to-treat population, number of subjects with data available (N=58 at Weeks 12 and 24)

[80] - Intent-to-treat population, number of subjects with data available (N=60 at Week 12; N=58 at Week24)

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	60 ^[81]			
Units: not applicable				
arithmetic mean (standard error)				
Week 12	5.569 (± 1.6467)			
Week 24	6.198 (± 1.696)			

Notes:

[81] - Intent-to-treat population, number of subjects with data available (N=60 at Weeks 12 and 24)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Functional assessment of Chronic Illness Therapy - fatigue (FACIT-F) subscale

End point title	Change from baseline in Functional assessment of Chronic Illness Therapy - fatigue (FACIT-F) subscale
End point description:	
End point type	Secondary
End point timeframe: from baseline till Week 24	

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61 ^[82]	65 ^[83]	58 ^[84]	61 ^[85]
Units: not applicable				
arithmetic mean (standard error)				
Week 12	11.014 (± 1.3593)	8.63 (± 1.0465)	10.884 (± 1.5424)	9.389 (± 1.3706)
Week 24	12.446 (± 1.5687)	10.439 (± 1.2157)	13.374 (± 1.5621)	12.381 (± 1.5193)

Notes:

[82] - Intent-to-treat population, number of subjects with data available (N=61 at Week 12; N=58 at Week24)

[83] - Intent-to-treat population, number of subjects with data available (N=65 at Week 12; N=62 at Week24)

[84] - Intent-to-treat population, number of subjects with data available (N=58 at Weeks 12 and 24)

[85] - Intent-to-treat population, number of subjects with data available (N=61 at Weeks 12 and 24)

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	62 ^[86]			
Units: not applicable				
arithmetic mean (standard error)				
Week 12	6.381 (± 1.2026)			
Week 24	6.712 (± 1.4651)			

Notes:

[86] - Intent-to-treat population, number of subjects with data available (N=60 at Week 12; N=62 at Week24)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: ALX-0061 concentration in serum

End point title	Pharmacokinetics: ALX-0061 concentration in serum ^[87]
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End point description:

End point type	Secondary
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End point timeframe:

at Week 12 and Week 24 visits

Notes:

[87] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: ALX-0061 concentrations were only measured in samples of subjects randomized to any of the ALX-0061 treatment arms.

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[88]	70 ^[89]	68 ^[90]	69 ^[91]
Units: microgram(s)/millilitre				
geometric mean (geometric coefficient of variation)				
Week 12	0.163 (± 3.7)	1.79 (± 3.08)	19.9 (± 1.56)	32.1 (± 1.43)
Week 24	0.122 (± 2.56)	1.64 (± 3.11)	20.9 (± 1.5)	35.2 (± 1.37)

Notes:

[88] - PK population

[89] - PK population

[90] - PK population

[91] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics: Concentrations of soluble interleukin-6 receptor (sIL-6R)

End point title	Pharmacodynamics: Concentrations of soluble interleukin-6 receptor (sIL-6R)
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End point description:

Values below the limit of quantification are imputed with the lower limit of quantification (LLOQ).

End point type	Secondary
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End point timeframe:

from baseline till Week 24

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[92]	70 ^[93]	68 ^[94]	69 ^[95]
Units: ng/mL				
arithmetic mean (standard error)				
Baseline	26.9 (± 0.995)	29.2 (± 1.04)	27.7 (± 0.78)	28.9 (± 1.05)
Week 12	166 (± 16.7)	420 (± 21)	519 (± 16.8)	488 (± 16.8)
Week 24	150 (± 12.9)	422 (± 17.8)	484 (± 16.3)	487 (± 14.3)

Notes:

[92] - Safety population

[93] - Safety population

[94] - Safety population

[95] - Safety population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[96]			
Units: ng/mL				
arithmetic mean (standard error)				
Baseline	28.9 (± 1.1)			
Week 12	52.9 (± 14.1)			
Week 24	35.4 (± 6.6)			

Notes:

[96] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with development of a treatment-emergent anti-drug antibody response

End point title	Number of subjects with development of a treatment-emergent anti-drug antibody response
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End point description:

End point type	Secondary
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End point timeframe:
from baseline till follow-up

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[97]	70 ^[98]	68 ^[99]	69 ^[100]
Units: subjects	9	16	31	33

Notes:

[97] - Safety population

[98] - Safety population

[99] - Safety population

[100] - Safety population

End point values	Placebo q2w + MTX	ALX-0061 total		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	69 ^[101]	276 ^[102]		
Units: subjects	13	89		

Notes:

[101] - Safety population

[102] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse event(s) by severity

End point title	Number of subjects with treatment-emergent adverse event(s) by severity
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End point description:

End point type	Secondary
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End point timeframe:

from baseline till Week 24 or Early Termination Visit

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[103]	70 ^[104]	68 ^[105]	69 ^[106]
Units: subjects				
mild	21	28	23	20
moderate	15	12	19	20
severe	6	4	2	4

Notes:

[103] - Safety population

[104] - Safety population

[105] - Safety population

[106] - Safety population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[107]			
Units: subjects				
mild	20			
moderate	14			
severe	2			

Notes:

[107] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent adverse events by severity

End point title	Number of treatment-emergent adverse events by severity
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End point description:

End point type	Secondary
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End point timeframe:

from baseline till Week 24 or the Early Termination visit

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[108]	70 ^[109]	68 ^[110]	69 ^[111]
Units: Events				
mild	66	78	66	56
moderate	34	24	26	40
severe	6	5	4	5

Notes:

[108] - Safety population

[109] - Safety population

[110] - Safety population

[111] - Safety population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[112]			
Units: Events				
mild	49			
moderate	22			

severe	2			
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Notes:

[112] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-related treatment-emergent adverse event(s)

End point title	Number of subjects with treatment-related treatment-emergent adverse event(s)
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End point description:

End point type	Secondary
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End point timeframe:

from baseline till Week 24 or the Ealy termination visit

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[113]	70 ^[114]	68 ^[115]	69 ^[116]
Units: subjects	26	25	26	25

Notes:

[113] - Safety population

[114] - Safety population

[115] - Safety population

[116] - Safety population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[117]			
Units: subjects	18			

Notes:

[117] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-related treatment-emergent adverse events

End point title	Number of treatment-related treatment-emergent adverse events
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End point description:

End point type	Secondary
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End point timeframe:
from baseline till Week 24 or early termination visit

End point values	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX	ALX-0061 225 mg q2w + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69 ^[118]	70 ^[119]	68 ^[120]	69 ^[121]
Units: events	55	52	46	47

Notes:

[118] - Safety population

[119] - Safety population

[120] - Safety population

[121] - Safety population

End point values	Placebo q2w + MTX			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[122]			
Units: events	21			

Notes:

[122] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first study drug intake until the Week 24 or Early Termination visit. Only safety data through Week 24 is reported as 256 of the 293 subjects who completed the 24-week treatment period rolled-over to the OLE Study and did not perform the FU visit.

Adverse event reporting additional description:

4 subjects had SAEs during the FU period, ie, 2 subjects in the 150 mg q4w group (pharyngitis [possibly related] and pneumonia [not related] in 1 subject each) and 2 subjects in the 225 mg q2w group (one with staphylococcal sepsis and staphylococcal intervertebral discitis [both possibly related] and one with large intestine perforation [related]).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	ALX-0061 75 mg q4w + MTX
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Reporting group description:

ALX-0061 75 mg every 4 weeks + MTX (at a stable dose and route) from baseline through Week 24

Reporting group title	ALX-0061 150 mg q4w + MTX
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Reporting group description:

ALX-0061 150 mg every 4 weeks + MTX (at a stable dose and route) from baseline through Week 24

Reporting group title	ALX-0061 150 mg q2w + MTX
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Reporting group description:

ALX-0061 150 mg every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24

Reporting group title	ALX-0061 225 mg q2w + MTX
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Reporting group description:

ALX-0061 225 mg every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24

Reporting group title	Placebo q2w + MTX
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Reporting group description:

placebo every 2 weeks + MTX (at a stable dose and route) from baseline through Week 24

Serious adverse events	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 69 (7.25%)	4 / 70 (5.71%)	0 / 68 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian adenoma			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Tendon rupture			
subjects affected / exposed	0 / 69 (0.00%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Cytopenia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 69 (0.00%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 69 (0.00%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ALX-0061 225 mg q2w + MTX	Placebo q2w + MTX	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 69 (1.45%)	4 / 69 (5.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian adenoma			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tendon rupture			

subjects affected / exposed	0 / 69 (0.00%)	2 / 69 (2.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Cytopenia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 69 (1.45%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ALX-0061 75 mg q4w + MTX	ALX-0061 150 mg q4w + MTX	ALX-0061 150 mg q2w + MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 69 (60.87%)	43 / 70 (61.43%)	44 / 68 (64.71%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 69 (2.90%)	2 / 70 (2.86%)	2 / 68 (2.94%)
occurrences (all)	3	2	2
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 69 (2.90%)	2 / 70 (2.86%)	1 / 68 (1.47%)
occurrences (all)	2	2	1
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 3	2 / 70 (2.86%) 2	3 / 68 (4.41%) 3
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 7	2 / 70 (2.86%) 2	0 / 68 (0.00%) 0
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5	5 / 70 (7.14%) 7	7 / 68 (10.29%) 8
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 7	2 / 70 (2.86%) 2	3 / 68 (4.41%) 3
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4	5 / 70 (7.14%) 5	2 / 68 (2.94%) 2
Pharyngitis subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2	6 / 70 (8.57%) 6	3 / 68 (4.41%) 4
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2	7 / 70 (10.00%) 7	4 / 68 (5.88%) 6

Non-serious adverse events	ALX-0061 225 mg q2w + MTX	Placebo q2w + MTX	
Total subjects affected by non-serious adverse events subjects affected / exposed	44 / 69 (63.77%)	34 / 69 (49.28%)	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 7	0 / 69 (0.00%) 0	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 6	0 / 69 (0.00%) 0	
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5	1 / 69 (1.45%) 1	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	0 / 69 (0.00%) 0	
General disorders and administration site conditions Injection site erythema subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 3	0 / 69 (0.00%) 0	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 3 4 / 69 (5.80%) 4 1 / 69 (1.45%) 1	3 / 69 (4.35%) 3 6 / 69 (8.70%) 6 0 / 69 (0.00%) 0	
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 6	4 / 69 (5.80%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2015	<ul style="list-style-type: none">• Assessment of C-telopeptide pyridinoline crosslinks of Type I collagen (ICTP) was removed, as the commercially available Enzyme-linked immunosorbent assay (ELISAs) for ICTP were not adequate.• Inclusion criterion on active RA was updated to allow inclusion of subjects with C-reactive protein (CRP) > 1.0 × upper limit of normal (ULN) at screening.• Exclusion criterion on previously received approved or investigational biological or targeted synthetic Disease-modifying antirheumatic drug (DMARD) therapies for RA was updated with details about subjects who previously received rituximab.• Pregnancy testing was clarified to confirm that it applied only to women of childbearing potential.• CRP or fibrinogen results were specified for unblinding in case of an alert and at screening (because these results are required at screening to assess subjects' eligibility).• Inclusion criterion 8 was updated with details about the inclusion of subjects with latent tuberculosis who have a positive Interferon-gamma release assay (IGRA) test and have completed appropriate treatment.• High-potency opioid analgesics were specified as prohibited medication during subjects' participation in the study.• The Investigator was directed to refer to the CTCAE v4.0 criteria to assess the severity of adverse events (AEs) related to laboratory abnormalities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none reported

Notes: