Clinical trial results:
A Phase IIb Multicenter, Randomized, Double-blind Study of ALX-0061 Administered Subcutaneously as Monotherapy, in Subjects with Moderate to Severe Rheumatoid Arthritis who are Intolerant to Methotrexate or for whom Continued Methotrexate Treatment is Inappropriate

Summary

EudraCT number	2014-003012-36
Trial protocol	BE DE HU CZ ES BG
Global end of trial date	19 July 2016

Results information

Result version number	v1 (current)
This version publication date	20 July 2017
First version publication date	20 July 2017

Trial information

Trial identification

Sponsor protocol code	ALX0061-C202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02287922
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	14 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2016
Global end of trial reached?	Yes
Global end of trial date	19 July 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 monotherapy administered subcutaneously (s.c.) to subjects with active rheumatoid arthritis (RA).
Subjects randomized to one of the 3 ALX-0061 treatment groups who completed the 12-week assessment period 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 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 adhered to throughout the study.

Background therapy: -

Evidence for comparator:

Tocilizumab (TCZ). The open-label treatment with TCZ s.c. was not intended to be an active comparator but to provide parallel efficacy and safety data for TCZ in the same RA population.

Actual start date of recruitment	18 March 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	Poland: 36
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 19
Country: Number of subjects enrolled	Moldova, Republic of: 29
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	Georgia: 46
Country: Number of subjects enrolled	Mexico: 36
Country: Number of subjects enrolled	United States: 16

Worldwide total number of subjects	251
EEA total number of subjects	89

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)	218
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 251 subjects were recruited at 58 sites located in Europe (42 sites; 199 subjects), Latin America (6 sites; 36 subjects) and North America (10 sites; 16 subjects). Consent was obtained from the first subject on 18 Mar 2015; the last subject completed the final visit in on 19 Jul 2016.

Pre-assignment

Screening details:

Of the 599 subjects screened, 348 were screen failures and 251 subjects were randomly assigned to treatment (Intent-to-treat population). All subjects enrolled received study medication and were included in the safety population. All subjects who received at least one dose of ALX-0061were 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 150 mg q4w

Arm description:

ALX-0061 150 mg every 4 weeks from baseline through Week 12 + placebo every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 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

Arm description:

ALX-0061 150 mg every 2 weeks from baseline through Week 12 + placebo every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 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
Arm description:	
ALX-0061 225 mg every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 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	TCZ 162 mg q1w or q2w
Arm description:	
Open-label TCZ. Injections were to be performed q1w or q2w depending on the approved label per region (last injection was administered at Week 10 or Week 11, depending on the dose regimen).	
Arm type	collection of parallel efficacy and safety data
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	Actemra, RoActemra
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
subcutaneous injections (162 mg of TCZ [RoActemra – Actemra]) in the lower part of the abdomen below the navel (belly button).	

Number of subjects in period 1	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w
Started	62	62	63
Completed	59	60	56
Not completed	3	2	7
Sponsor's decision	-	-	-
Consent withdrawn by subject	1	1	1
Adverse event, non-fatal	1	1	3
Other	1	-	2
Lost to follow-up	-	-	1

Number of subjects in period 1	TCZ 162 mg q1w or q2w

Started	64
Completed	57
Not completed	7
Sponsor's decision	1
Consent withdrawn by subject	2
Adverse event, non-fatal	4
Other	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	ALX-0061 150 mg q4w
Reporting group description:	
ALX-0061 150 mg every 4 weeks from baseline through Week 12 + placebo every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 visit.	
Reporting group title	ALX-0061 150 mg q2w
Reporting group description:	
ALX-0061 150 mg every 2 weeks from baseline through Week 12 + placebo every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 visit.	
Reporting group title	ALX-0061 225 mg q2w
Reporting group description:	
ALX-0061 225 mg every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 visit.	
Reporting group title	TCZ 162 mg q1w or q2w
Reporting group description:	
Open-label TCZ. Injections were to be performed q1w or q2w depending on the approved label per region (last injection was administered at Week 10 or Week 11, depending on the dose regimen).	

Reporting group values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w
Number of subjects	62	62	63
Age categorical			
Units: Subjects			
Adults (18-64 years)	50	54	56
From 65-84 years	12	8	7
Age continuous			
Units: years			
arithmetic mean	53	51.2	51.3
standard deviation	± 12.25	± 12.05	± 11.81
Gender categorical			
Units: Subjects			
Female	49	53	54
Male	13	9	9

Reporting group values	TCZ 162 mg q1w or q2w	Total	
Number of subjects	64	251	
Age categorical			
Units: Subjects			
Adults (18-64 years)	58	218	
From 65-84 years	6	33	
Age continuous			
Units: years			
arithmetic mean	50		
standard deviation	± 12.26	-	
Gender categorical			
Units: Subjects			
Female	56	212	
Male	8	39	

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 150 q4w, ALX-0061 150 mg q2w and ALX-0061 225 mg q2w groups

Reporting group values	ALX-0061 total		
Number of subjects	187		
Age categorical Units: Subjects			
Adults (18-64 years)	160		
From 65-84 years	27		
Age continuous Units: years			
arithmetic mean	51.8		
standard deviation	± 12		
Gender categorical Units: Subjects			
Female	156		
Male	31		

End points

End points reporting groups

Reporting group title	ALX-0061 150 mg q4w
Reporting group description:	
ALX-0061 150 mg every 4 weeks from baseline through Week 12 + placebo every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 visit.	
Reporting group title	ALX-0061 150 mg q2w
Reporting group description:	
ALX-0061 150 mg every 2 weeks from baseline through Week 12 + placebo every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 visit.	
Reporting group title	ALX-0061 225 mg q2w
Reporting group description:	
ALX-0061 225 mg every 2 weeks from baseline through Week 12. The last injection with study drug was administered at the Week 10 visit.	
Reporting group title	TCZ 162 mg q1w or q2w
Reporting group description:	
Open-label TCZ. Injections were to be performed q1w or q2w depending on the approved label per region (last injection was administered at Week 10 or Week 11, depending on the dose regimen).	
Subject analysis set title	ALX-0061 total
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects randomized to the ALX0061 150 q4w, ALX-0061 150 mg q2w and ALX-0061 225 mg q2w groups	

Primary: Percentage of subjects with American College of Rheumatology 20 (ACR20) response at Week 12

End point title	Percentage of subjects with American College of Rheumatology 20 (ACR20) response at Week 12[1]
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	

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: The primary endpoint was analyzed using descriptive statistics (frequency, percentage) which were presented by treatment group on the intent-to-treat population. Subjects with missing ACR20 response at Week 12 were treated as non responders (non-responder imputation [NRI] approach).

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[2]	62[3]	63[4]	64[5]
Units: percent responders	73	77	81	78

Notes:

[2] - Intent-to-treat population

[3] - Intent-to-treat population

[4] - Intent-to-treat population

[5] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with ACR50 response at Week 12

End point title	Proportion of subjects with ACR50 response at Week 12

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[6]	62[7]	63[8]	64[9]
Units: percent responders	44	37	49	45

Notes:

[6] - Intent-to-treat population

[7] - Intent-to-treat population

[8] - Intent-to-treat population

[9] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with ACR70 response at Week 12

End point title	Proportion of subjects with ACR70 response at Week 12

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[10]	62[11]	63[12]	64[13]
Units: percent responders	16	24	21	23

Notes:

[10] - Intent-to-treat population

[11] - Intent-to-treat population

[12] - Intent-to-treat population

[13] - 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 using 28 joint counts (DAS28) using C-reactive protein (CRP) at Week 12

End point title	Proportion of subjects with Low Disease Activity (LDA) using Disease Activity Score using 28 joint counts (DAS28) using C-reactive protein (CRP) at Week 12

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[14]	62[15]	63[16]	64[17]
Units: percent	42	56	60	44

Notes:

[14] - Intent-to-treat population

[15] - Intent-to-treat population

[16] - Intent-to-treat population

[17] - 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) at Week 12

End point title	Proportion of subjects with LDA using DAS28 using Erythrocyte Sedimentation Rate (ESR) at Week 12

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 Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[18]	62[19]	63[20]	64[21]
Units: percent	42	52	54	31

Notes:

[18] - Intent-to-treat population

[19] - Intent-to-treat population

[20] - Intent-to-treat population

[21] - 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) at Week 12

End point title	Proportion of subjects with LDA using Simplified Disease Activity Index (SDAI) at Week 12

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 Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[22]	62[23]	63[24]	64[25]
Units: percent	37	44	52	34

Notes:

[22] - Intent-to-treat population

[23] - Intent-to-treat population

[24] - Intent-to-treat population

[25] - 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) at Week 12

End point title	Proportion of subjects with LDA using Clinical Disease Activity Index (CDAI) at Week 12

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 Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[26]	62[27]	63[28]	64[29]
Units: percent	37	34	51	33

Notes:

[26] - Intent-to-treat population

[27] - Intent-to-treat population

[28] - Intent-to-treat population

[29] - 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 at Week 12

End point title	Proportion of subjects with European League Against Rheumatism (EULAR) (CRP) good response at Week 12

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[30]	62[31]	63[32]	64[33]
Units: percent responders	40	55	60	44

Notes:

[30] - Intent-to-treat population

[31] - Intent-to-treat population

[32] - Intent-to-treat population

[33] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in remission using DAS28 (ESR) at Week 12

End point title	Proportion of subjects in remission using DAS28 (ESR) at Week 12

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[34]	62[35]	63[36]	64[37]
Units: percent	34	21	40	25

Notes:

[34] - Intent-to-treat population

[35] - Intent-to-treat population

[36] - Intent-to-treat population

[37] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in remission using SDAI at Week 12

End point title	Proportion of subjects in remission using SDAI at Week 12

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[38]	62[39]	63[40]	64[41]
Units: percent	8	5	8	11

Notes:

[38] - Intent-to-treat population

[39] - Intent-to-treat population

[40] - Intent-to-treat population

[41] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in remission using CDAI at Week 12

End point title	Proportion of subjects in remission using CDAI at Week 12

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[42]	62[43]	63[44]	64[45]
Units: percent	10	5	6	9

Notes:

[42] - Intent-to-treat population

[43] - Intent-to-treat population

[44] - Intent-to-treat population

[45] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in remission using Boolean defined remission criteria at Week 12

End point title	Proportion of subjects in remission using Boolean defined remission criteria at Week 12

End point description:

This endpoint was analyzed using non-responder imputation (NRI), i.e., subjects with missing response at Week 12 were treated as non responders.

End point type	Secondary

End point timeframe:

at Week 12 visit

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[46]	62[47]	63[48]	64[49]
Units: percent	3	5	6	6

Notes:

[46] - Intent-to-treat population

[47] - Intent-to-treat population

[48] - Intent-to-treat population

[49] - 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) at Week 12

End point title	Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 12

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 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61[50]	60[51]	59[52]	64[53]
Units: not applicable				
arithmetic mean (standard error)	-0.541 (± 0.0809)	-0.746 (± 0.0935)	-0.817 (± 0.0802)	-0.689 (± 0.0811)

Notes:

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

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

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

[53] - 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) at Week 12

End point title	Change from baseline in physical component score of Short Form Health Survey (SF-36) at Week 12

End point description:

End point type	Secondary

End point timeframe:

from baseline till Week 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[54]	60[55]	56[56]	54[57]
Units: not applicable				
arithmetic mean (standard error)	7.808 (± 0.8533)	7.979 (± 1.1895)	8.861 (± 1.0818)	7.611 (± 0.9562)

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mental component score of Short Form Health Survey (SF-36) at Week 12

End point title	Change from baseline in mental component score of Short Form Health Survey (SF-36) at Week 12

End point description:

End point type	Secondary

End point timeframe:
from baseline till Week 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[58]	60[59]	56[60]	55[61]
Units: not applicable				
arithmetic mean (standard error)	5.49 (± 1.221)	8.836 (± 1.5243)	8.913 (± 1.3903)	6.156 (± 1.3192)

Notes:
[58] - Intent-to-treat population, number of subjects with data available
[59] - Intent-to-treat population, number of subjects with data available
[60] - Intent-to-treat population, number of subjects with data available
[61] - Intent-to-treat population, number of subjects with data available

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Functional assessment of Chronic Illness Therapy - fatigue (FACIT-F) subscale at Week 12

End point title	Change from baseline in Functional assessment of Chronic Illness Therapy - fatigue (FACIT-F) subscale at Week 12

End point description:

End point type	Secondary

End point timeframe:
from baseline till Week 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58[62]	60[63]	56[64]	57[65]
Units: not applicable				
arithmetic mean (standard error)	7.832 (± 1.3438)	11.41 (± 1.53)	12.996 (± 1.3702)	8.971 (± 1.4461)

Notes:

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

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

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

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

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)

End point description:

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

End point type	Secondary

End point timeframe:

from baseline till Week 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[66]	62[67]	63[68]	64[69]
Units: ng/mL				
arithmetic mean (standard error)				
Baseline	33 (± 4.65)	42.3 (± 8.71)	30.9 (± 3.72)	31 (± 2.54)
Week 12	376 (± 21.6)	460 (± 19.9)	459 (± 18.8)	269 (± 11.1)

Notes:

[66] - Safety population

[67] - Safety population

[68] - Safety population

[69] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: ALX-0061 concentration in serum over time

End point title	Pharmacokinetics: ALX-0061 concentration in serum over

End point description:

End point type	Secondary

End point timeframe:

at Week 12 visit

Notes:

[70] - 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 analyzed in samples from subjects randomized to one of the ALX-0061 treatment groups.

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62[71]	62[72]	63[73]	
Units: microgram(s)/millilitre				
geometric mean (geometric coefficient of variation)				
Week 12	1.4 (± 3.61)	18.4 (± 2.95)	27.9 (± 2.53)	

Notes:

[71] - PK population

[72] - PK population

[73] - PK 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[74]

End point description:

End point type	Secondary

End point timeframe:

from baseline till follow-up (FU)

Notes:

[74] - 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: Anti-drug antibody repsonses were only analyzed in samples from subjects randomized to one of the ALX-0061 treatment groups.

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	ALX-0061 total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	62[75]	62[76]	63[77]	187[78]
Units: subjects	7	25	26	58

Notes:

[75] - Safety population

[76] - Safety population

[77] - Safety population

[78] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects categorized as NAb positive on treatment

End point title	Number of subjects categorized as NAb positive on

End point description:

End point type	Secondary

End point timeframe:

from baseline till FU

Notes:

[79] - 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: Neutralizing antibody repsonses were only analyzed in samples from subjects randomized to one of the ALX-0061 treatment groups.

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	ALX-0061 total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	62[80]	62[81]	63[82]	187[83]
Units: subjects	4	3	4	11

Notes:

[80] - Safety population

[81] - Safety population

[82] - Safety population

[83] - Safety population

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with treatment-emergent adverse event by severity

End point description:

End point type	Secondary

End point timeframe:

from baseline till Week 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[84]	62[85]	63[86]	64[87]
Units: subjects				
mild	22	18	21	19
moderate	12	13	9	10
severe	0	2	1	2

Notes:
[84] - Safety population
[85] - Safety population
[86] - Safety population
[87] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent adverse event by severity

End point title	Number of treatment-emergent adverse event by severity

End point description:

End point type	Secondary

End point timeframe:
from baseline till Week 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[88]	62[89]	63[90]	64[91]
Units: treatment-emergent adverse events				
mild	46	75	84	47
moderate	18	22	15	15
severe	0	2	3	2

Notes:
[88] - Safety population
[89] - Safety population
[90] - Safety population
[91] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a treatment-related treatment-emergent adverse event

End point title	Number of subjects with a treatment-related treatment-emergent adverse event

End point description:
treatment related = considered at least possibly related to study drug by the Investigator

End point type	Secondary

End point timeframe:
from baseline till Week 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[92]	62[93]	63[94]	64[95]
Units: subjects	21	20	21	20

Notes:

[92] - Safety population

[93] - Safety population

[94] - Safety population

[95] - Safety population

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of treatment-related treatment-emergent adverse event

End point description:

treatment related = considered at least possibly related to study drug by the Investigator

End point type	Secondary

End point timeframe:

from baseline till Week 12

End point values	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w	TCZ 162 mg q1w or q2w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62[96]	62[97]	63[98]	64[99]
Units: treatment-emergent adverse events	46	53	64	32

Notes:

[96] - Safety population

[97] - Safety population

[98] - Safety population

[99] - 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 Week 12 or ET visit. Only safety data through Week 12 is reported as 148 of the 174 subjects who completed the 12-week treatment period could roll over to OLE study ALX0061-C203 and did not perform the FU visit.

Adverse event reporting additional description:

In the FU period (performed by 55 subjects in the TCZ group and 26 subjects in the ALX-0061 groups), 2 serious adverse events (SAEs) were reported, i.e., chronic obstructive pulmonary disease (considered not related) in 1 subject in the ALX-0061 150 mg q4w group and dehydration (considered not related) in 1 subject in the ALX-0061 225 mg q2w group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	ALX-0061 150 mg q4w

Reporting group description:

ALX-0061 150 mg every 4 weeks from baseline through Week 12 + placebo every 2 weeks from baseline through Week 12

Reporting group title	ALX-0061 150 mg q2w

Reporting group description:

ALX-0061 150 mg every 2 weeks from baseline through Week 12 + placebo every 2 weeks from baseline through Week 12

Reporting group title	ALX-0061 225 mg q2w

Reporting group description:

ALX-0061 225 mg every 2 weeks from baseline through Week 12

Reporting group title	TCZ 162 mg q1w or q2w

Reporting group description:

Open-label TCZ according to the TCZ dosing regimen approved per region

Serious adverse events	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 62 (0.00%)	0 / 63 (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
Erysipelas			

subjects affected / exposed	0 / 62 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nail bed infection bacterial			
subjects affected / exposed	0 / 62 (0.00%)	0 / 62 (0.00%)	0 / 63 (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

Serious adverse events	TCZ 162 mg q1w or q2w		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 64 (3.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nail bed infection bacterial			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ALX-0061 150 mg q4w	ALX-0061 150 mg q2w	ALX-0061 225 mg q2w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 62 (33.87%)	20 / 62 (32.26%)	20 / 63 (31.75%)
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	4 / 63 (6.35%)
occurrences (all)	1	0	5
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	4 / 62 (6.45%)	1 / 62 (1.61%)	0 / 63 (0.00%)
occurrences (all)	4	1	0
Neutropenia			
subjects affected / exposed	4 / 62 (6.45%)	3 / 62 (4.84%)	0 / 63 (0.00%)
occurrences (all)	5	3	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	4 / 62 (6.45%)	7 / 62 (11.29%)	5 / 63 (7.94%)
occurrences (all)	7	10	20
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 62 (0.00%)	4 / 62 (6.45%)	1 / 63 (1.59%)
occurrences (all)	0	4	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	2 / 62 (3.23%)	5 / 62 (8.06%)	7 / 63 (11.11%)
occurrences (all)	2	5	7

Non-serious adverse events	TCZ 162 mg q1w or q2w		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 64 (28.13%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 64 (3.13%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	5 / 64 (7.81%)		
occurrences (all)	5		
General disorders and administration site conditions			

Injection site erythema subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2015	• Assessment of C-telopeptide pyridinoline crosslinks of Type 1 collagen (ICTP) was removed, as the commercially available Enzyme Linked Immunosorbent Assays (ELISAs) for ICTP were not adequate. • The word "current" was deleted from the inclusion criterion on previous treatment with methotrexate (MTX) as the current MTX treatment was not feasible, because the screening period was only 3 weeks long and the protocol required a wash-out of at least 4 weeks. In addition, the inclusion criterion on active rheumatoid arthritis (RA) was updated to allow inclusion of subjects with C-reactive protein (CRP) > 1.0 × upper limit of normal (ULN) at screening. • The exclusion criterion on previous treatment with Disease Modifying Antirheumatic Drugs (DMARDs)/systemic immunosuppressives was updated to correct an error about the use of hydroxychloroquine and chloroquine. In addition, the exclusion criterion on previously received approved or investigational biological or targeted synthetic DMARD therapies for RA was updated to add details about subjects who previously received rituximab. • IWRS notification was removed from the Schedule of Assessments as this notification was a copy error from protocol ALX0061-C201. • Pregnancy testing was clarified to confirm that such testing applied only to women of childbearing potential. • CRP or fibrinogen results were specified for unblinding in case of an alert and at screening. • Inclusion criterion 9 was updated to add details about the inclusion of subjects with latent tuberculosis (TB) who have a positive Interferon-Gamma Release Assays (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: