Clinical trial results:
A Phase II Multicenter, Open-Label Extension Study Assessing the Long-Term Efficacy and Safety of Subcutaneous ALX-0061 in Subjects with Moderate to Severe Rheumatoid Arthritis who Have Completed One of the Preceding Phase IIb Studies with ALX-0061

Summary

EudraCT number	2014-003034-42
Trial protocol	HU DE ES BG BE
Global end of trial date	23 August 2018

Results information

Result version number	v1 (current)
This version publication date	01 May 2019
First version publication date	01 May 2019

Trial information

Trial identification

Sponsor protocol code	ALX0061-C203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02518620
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ablynx NV
Sponsor organisation address	Technologiepark 21, Zwijnaarde, Belgium, 9052
Public contact	Medical Monitor, Ablynx, +32 (0)9 262 00 00, clinicaltrials@ablynx.com
Scientific contact	Medical Monitor, Ablynx, +32 (0)9 262 00 00, 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	09 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2018
Global end of trial reached?	Yes
Global end of trial date	23 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term efficacy and safety of ALX-0061 administered subcutaneously (s.c.) to subjects with active Rheumatoid Arthritis (RA).

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:

Eligible subjects from the preceding Phase IIb study ALX0061-C201 (combination therapy study with ALX-0061 and MTX) continued their MTX treatment throughout this study.

Evidence for comparator:

Not applicable

Actual start date of recruitment	13 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 105
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Bulgaria: 38
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Georgia: 65
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 21
Country: Number of subjects enrolled	Mexico: 73
Country: Number of subjects enrolled	Moldova, Republic of: 22
Country: Number of subjects enrolled	Serbia: 32
Worldwide total number of subjects	406
EEA total number of subjects	193

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)	341
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 406 subjects was enrolled at 56 sites located in Europe (48 sites, 333 subjects) and Latin America (8 sites, 73 subjects). Consent was obtained from the first subject on 13 July 2015; the last subject completed the final visit on 23 August 2018.

Pre-assignment

Screening details:

A total of 472 subjects completed the entire treatment and assessment period of the preceding Phase IIb studies (placebo and ALX-0061 treatment arms only). Of these, 406 subjects were enrolled in this study. All screened subjects were included in the Intent-to-observe (ITO) Population. Overall, 405 subjects were included in the Safety Population.

Period 1

Period 1 title	Overall Study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

As this was an open-label extension study, blinding was not required.

Arms

Are arms mutually exclusive?	Yes
Arm title	ALX-0061 150 mg q2w + MTX (C201 All Subjects)

Arm description:

ALX-0061 150 mg s.c. q2w + MTX

Arm type	Experimental
Investigational medicinal product name	ALX-0061
Investigational medicinal product code	ALX-0061
Other name	Vobarilizumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received ALX-0061 150 mg s.c. injections, beginning at Week 0 and q2w thereafter, up to and including Week 102. Subjects from the preceding study ALX0061-C201 also continued their MTX treatment.

Arm title	ALX-0061 150 mg q2w (C202 All Subjects)

Arm description:

ALX-0061 150 mg s.c. q2w

Arm type	Experimental
Investigational medicinal product name	ALX-0061
Investigational medicinal product code	ALX-0061
Other name	Vobarilizumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received ALX-0061 150 mg s.c. injections, beginning at Week 0 and q2w thereafter, up to and including Week 102.

Number of subjects in period 1	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)
Started	257	149
Completed	205	123
Not completed	52	26
Adverse event, serious fatal	1	-
Relocation	2	1
Sponsor's decision	-	3
Physician decision	1	1
Consent withdrawn by subject	17	9
Adverse event, non-fatal	23	11
Pregnancy	1	-
Non-compliance with study drug	1	-
Lost to follow-up	1	1
Pregnancy wish	3	-
Lack of efficacy	2	-

Baseline characteristics

Reporting groups	
Reporting group title	ALX-0061 150 mg q2w + MTX (C201 All Subjects)
Reporting group description: ALX-0061 150 mg s.c. q2w + MTX	
Reporting group title	ALX-0061 150 mg q2w (C202 All Subjects)
Reporting group description: ALX-0061 150 mg s.c. q2w	

Reporting group values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	Total
Number of subjects	257	149	406
Age categorical Units: Subjects			
Adults (18-64 years)	213	128	341
From 65-84 years	44	21	65
Age continuous Units: years			
arithmetic mean	51.7	51.1	
standard deviation	± 12.26	± 12.01	-
Gender categorical Units: Subjects			
Female	217	124	341
Male	40	25	65

End points

End points reporting groups

Reporting group title	ALX-0061 150 mg q2w + MTX (C201 All Subjects)
Reporting group description: ALX-0061 150 mg s.c. q2w + MTX	
Reporting group title	ALX-0061 150 mg q2w (C202 All Subjects)
Reporting group description: ALX-0061 150 mg s.c. q2w	
Subject analysis set title	ALX-0061 150 mg q2w (C203 All Subjects)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects received ALX-0061 150 mg s.c. injections, beginning at Week 0 and q2w thereafter, up to and including Week 102. Subjects from the preceding study ALX0061-C201 also continued their MTX.	

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

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

End point description:

ACR20 response is defined as:
- 20% improvement in tender/painful joint count (68 joints) relative to baseline AND
- 20% improvement in swollen joint count (66 joints) relative to baseline AND
- 20% improvement in 3 of the following 5 areas relative to baseline:
  - Patient's Assessment of Pain (100 mm-VAS),
  - Patient's Global Assessment of Disease Activity (100 mm-VASPA),
  - Physician's Global Assessment of Disease Activity (100 mm-VASPHA),
  - Patient's assessment of physical function as measured by HAQ-DI,
  - C-reactive protein (CRP) level

ACR20 responses were measured at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 104.

End point type	Primary

End point timeframe:

At Weeks 0, 12, 48, and 104.

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: This study was an open label extension study. No inferential statistical analyses were performed. All statistical analyses are descriptive.

End point values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	257[2]	149[3]	406[4]	
Units: Percent				
Week 0	89	85	88	
Week 12	90	92	91	
Week 48	94	94	94	
Week 104	97	95	96	

Notes:

[2] - ITO Population
Number of subjects evaluated at:
W0: n=251
W12: n=246
W48: n=223

W104: n=199

[3] - ITO Population
Number of subjects evaluated at:
W0: n=149
W12: n=141
W48: n=134
W104: n=123

[4] - Number of subjects evaluated at:
W0: n=400
W12: n=387
W48: n=357
W104: n=322

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with ACR50 response

End point title	Percentage of subjects with ACR50 response[5]

End point description:

ACR50 responses are defined as:
- 50% improvement in tender/painful joint count (68 joints) relative to baseline AND
- 50% improvement in swollen joint count (66 joints) relative to baseline AND
- 50% improvement in 3 of the following 5 areas relative to baseline:
  - Patient's Assessment of Pain (100 mm-VAS),
  - Patient's Global Assessment of Disease Activity (100 mm-VASPA),
  - Physician's Global Assessment of Disease Activity (100 mm-VASPHA),
  - Patient's assessment of physical function as measured by HAQ-DI,
  - CRP level

ACR50 responses were measured at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 104.

End point type	Primary

End point timeframe:

At Weeks 0, 12, 48, and 104

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open label extension study. No inferential statistical analyses were performed. All statistical analyses are descriptive.

End point values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	257[6]	149[7]	406[8]	
Units: Percent				
Week 0	62	47	56	
Week 12	71	62	68	
Week 48	77	81	78	
Week 104	84	85	84	

Notes:

[6] - ITO Population
Number of subjects evaluated at:
W0:n=246
W12:n=244
W48:n=222
W104:n=198

[7] - ITO Population
Number of subjects evaluated at:

W0:n=148
W12:n=141
W48:n=134
W104:n=123
[8] - Number of subjects evaluated at:
W0: n=394
W12: n=385
W48: n=356
W104: n=321

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with ACR70 response

End point title	Percentage of subjects with ACR70 response[9]

End point description:

ACR70 responses are defined as:
- 70% improvement in tender/painful joint count (68 joints) relative to baseline AND
- 70% improvement in swollen joint count (66 joints) relative to baseline AND
- 70% improvement in 3 of the following 5 areas relative to baseline:
  - Patient's Assessment of Pain (100 mm-VAS),
  - Patient's Global Assessment of Disease Activity (100 mm-VASPA),
  - Physician's Global Assessment of Disease Activity (100 mm-VASPHA),
  - Patient's assessment of physical function as measured by HAQ-DI,
  - CRP level

ACR70 responses were measured at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 104.

End point type	Primary

End point timeframe:

At weeks 0, 12, 48, and 104

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open label extension study. No inferential statistical analyses were performed. All statistical analyses are descriptive.

End point values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	257[10]	149[11]	406[12]	
Units: Percent				
Week 0	34	22	30	
Week 12	44	36	41	
Week 48	61	50	57	
Week 104	69	72	70	

Notes:

[10] - ITO Population
Number of subjects evaluated at:
W0:n=249
W12:n=243
W48:n=221
W104:n=197
[11] - ITO Population
Number of subjects evaluated at:
W0:n=147
W12:n=141
W48:n=133
W104:n=123

[12] - Number of subjects evaluated at:
W0: n=396
W12: n=384
W48: n=354
W104: n=320

Statistical analyses

No statistical analyses for this end point

Primary: ACR-N Index of Improvement

End point title	ACR-N Index of Improvement[13]

End point description:

The ACR-N Index of Improvement is defined as the minimum of the following 3 criteria:
- The percent improvement from Week 0 in TJCs
- The percent improvement from Week 0 in SJCs
- The median percent improvement from Week 0 for the following 5 assessments:
  - Subject's assessment of pain (VAS)
  - Subject's global assessment of disease activity (VASPHA)
  - Physician's global assessment of disease activity (VASPHA)
  - Subject's assessment of physical function as measured by the HAQ-DI
  - CRP level

ACR-N Index of Improvement was measured at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 104.

End point type	Primary

End point timeframe:

At Weeks 0, 12, 48, and 104

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open label extension study. No inferential statistical analyses were performed. All statistical analyses are descriptive.

End point values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	257[14]	149[15]	406[16]	
Units: No unit				
arithmetic mean (standard error)				
Week 0	55.77 (± 1.703)	48.18 (± 2.171)	52.98 (± 1.351)	
Week 12	61.51 (± 1.643)	57.07 (± 2.181)	59.91 (± 1.315)	
Week 48	67.73 (± 1.691)	66.49 (± 2.048)	67.27 (± 1.306)	
Week 104	74.83 (± 1.554)	73.82 (± 2.171)	74.45 (± 1.265)	

Notes:

[14] - ITO Population
Number of subjects evaluated at:
W0:n=256
W12:n=252
W48:n=228
W104:n=205

[15] - ITO Population
Number of subjects evaluated at:

W0:n=149
W12:n=142
W48:n=135
W104:n=123
[16] - Number of subjects evaluated at:
W0: n=405
W12: n=394
W48: n=363
W104: n=328

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects in remission based on Disease Activity Score using 28 joint counts (DAS28) using estimated sedimentation rate (ESR)

End point title	Percentage of subjects in remission based on Disease Activity Score using 28 joint counts (DAS28) using estimated sedimentation rate (ESR)[17]

End point description:

DAS28(ESR) = (0.56 × √TJC28) + (0.28 × √SJC28) + (0.70 × ln[ESR]) + (0.014 × VASPA)
Remission = DAS28(ESR) < 2.6

Disease activity based on DAS28(ESR) was measured at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 104.

End point type	Primary

End point timeframe:

At Weeks 0, 12, 48, and 104.

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an open label extension study. No inferential statistical analyses were performed. All statistical analyses are descriptive.

End point values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	257[18]	149[19]	406[20]	
Units: Percent				
Week 0	40	34	38	
Week 12	57	49	54	
Week 48	63	53	59	
Week 104	74	69	72	

Notes:

[18] - ITO Population
Number of subjects evaluated at:
W0: n=253
W12: n=248
W48: n=220
W104: n=198
[19] - ITO Population
Number of subjects evaluated at:
W0: n=148
W12: n=138
W48: n=132
W104: n=121
[20] - Number of subjects evaluated at:
W0: n=401

W12: n=386
W48: n=352
W104: n=319

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with low disease activity based on DAS28(ESR)

End point title	Percentage of subjects with low disease activity based on DAS28(ESR)[21]

End point description:

DAS28(ESR) = (0.56 × √TJC28) + (0.28 × √SJC28) + (0.70 × ln[ESR]) + (0.014 × VASPA)
Low disease activity = 2.6 ≤ DAS28 ≤ 3.2

Disease activity based on DAS28(ESR) was measured at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 104.

End point type	Primary

End point timeframe:

At Weeks 0, 12, 48, and 104.

Notes:

[21] - 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: This study was an open label extension study. No inferential statistical analyses were performed. All statistical analyses are descriptive.

End point values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	257[22]	149[23]	406[24]	
Units: Percent				
Week 0	15	18	16	
Week 12	15	14	15	
Week 48	14	20	16	
Week 104	14	10	13	

Notes:

[22] - ITO Population
Number of subjects evaluated at:
W0: n=253
W12: n=248
W48: n=220
W104: n=198
[23] - ITO Population
Number of subjects evaluated at:
W0: n=148
W12: n=138
W48: n=132
W104: n=121
[24] - Number of subjects evaluated at:
W0: n=401
W12: n=386
W48: n=352
W104: n=319

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with DAS28 using C-reactive protein (CRP) < 2.6

End point title	Percentage of subjects with DAS28 using C-reactive protein (CRP) < 2.6[25]

End point description:

DAS28(CRP) = (0.56 × √TJC28) + (0.28 × √SJC28) + (0.36 × ln[CRP+1]) + (0.014 × VASPA) + 0.96
DAS28(CRP) < 2.6

Disease activity based on DAS28(CRP) was measured at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 104.

End point type	Primary

End point timeframe:

At Weeks 0, 12, 48, and 104.

Notes:

[25] - 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: This study was an open label extension study. No inferential statistical analyses were performed. All statistical analyses are descriptive.

End point values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	257[26]	149[27]	406[28]	
Units: Percent				
Week 0	39	33	37	
Week 12	60	51	57	
Week 48	67	58	64	
Week 104	78	75	77	

Notes:

[26] - ITO Population
Number of subjects evaluated at:
W0: n=256
W12: n=249
W48: n=228
W104: n=204

[27] - ITO Population
Number of subjects evaluated at:
W0: n=149
W12: n=142
W48: n=134
W104: n=123

[28] - Number of subjects evaluated at:
W0: n=405
W12: n=391
W48: n=362
W104: n=327

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with low disease activity based on DAS28(CRP)

End point title	Percentage of subjects with low disease activity based on DAS28(CRP)[29]

End point description:

DAS28(CRP) = (0.56 × √TJC28) + (0.28 × √SJC28) + (0.36 × ln[CRP+1]) + (0.014 × VASPA) + 0.96
Low disease activity = 2.6 ≤ DAS28 ≤ 3.2

Disease activity based on DAS28(CRP) was measured at Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, and 104.

End point type	Primary

End point timeframe:

At Weeks 0, 12, 48, and 104.

Notes:

[29] - 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: This study was an open label extension study. No inferential statistical analyses were performed. All statistical analyses are descriptive.

End point values	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	257[30]	149[31]	406[32]	
Units: Percent				
Week 0	21	23	21	
Week 12	16	16	16	
Week 48	18	19	18	
Week 104	14	16	15	

Notes:

[30] - ITO Population
Number of subjects evaluated at:
W0: n=256
W12: n=249
W48: n=228
W104: n=204

[31] - ITO Population
Number of subjects evaluated at:
W0: n=149
W12: n=142
W48: n=134
W104: n=123

[32] - Number of subjects evaluated at:
W0: n=405
W12: n=391
W48: n=362
W104: n=327

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of first study drug administration in study ALX0061-C203 until the subject's study completion/discontinuation date.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	ALX-0061 150 mg q2w + MTX (C201 All Subjects)

Reporting group description:

ALX-0061 150 mg s.c. q2w + MTX

Reporting group title	ALX-0061 150 mg q2w (C202 All Subjects)

Reporting group description:

ALX-0061 150 mg s.c. q2w

Reporting group title	ALX-0061 150 mg q2w (C203 All Subjects)

Reporting group description:

Subjects received ALX-0061 150 mg s.c. injections, beginning at Week 0 and q2w thereafter, up to and including Week 102. Subjects from the preceding study ALX0061-C201 also continued their MTX treatment.

Serious adverse events	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 257 (9.73%)	9 / 148 (6.08%)	34 / 405 (8.40%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	2	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			

subjects affected / exposed	0 / 257 (0.00%)	1 / 148 (0.68%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular seminoma (pure)			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 257 (0.00%)	1 / 148 (0.68%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	0 / 257 (0.00%)	1 / 148 (0.68%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 257 (0.00%)	1 / 148 (0.68%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 257 (0.39%)	1 / 148 (0.68%)	2 / 405 (0.49%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	2 / 257 (0.78%)	0 / 148 (0.00%)	2 / 405 (0.49%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 257 (0.00%)	1 / 148 (0.68%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 257 (0.00%)	1 / 148 (0.68%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 257 (0.39%)	2 / 148 (1.35%)	3 / 405 (0.74%)
occurrences causally related to treatment / all	1 / 1	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 257 (1.17%)	0 / 148 (0.00%)	3 / 405 (0.74%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess neck			
subjects affected / exposed	0 / 257 (0.00%)	1 / 148 (0.68%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal abscess			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Septic shock			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Staphylococcal sepsis			
subjects affected / exposed	1 / 257 (0.39%)	0 / 148 (0.00%)	1 / 405 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ALX-0061 150 mg q2w + MTX (C201 All Subjects)	ALX-0061 150 mg q2w (C202 All Subjects)	ALX-0061 150 mg q2w (C203 All Subjects)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	175 / 257 (68.09%)	100 / 148 (67.57%)	275 / 405 (67.90%)
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 257 (3.50%)	8 / 148 (5.41%)	17 / 405 (4.20%)
occurrences (all)	9	8	17
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 257 (1.56%)	9 / 148 (6.08%)	13 / 405 (3.21%)
occurrences (all)	5	13	18
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	14 / 257 (5.45%)	11 / 148 (7.43%)	25 / 405 (6.17%)
occurrences (all)	28	23	51
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 257 (4.67%)	8 / 148 (5.41%)	20 / 405 (4.94%)
occurrences (all)	12	8	20
Infections and infestations			

Upper respiratory tract infection			
subjects affected / exposed	23 / 257 (8.95%)	12 / 148 (8.11%)	35 / 405 (8.64%)
occurrences (all)	31	13	44
Nasopharyngitis			
subjects affected / exposed	17 / 257 (6.61%)	11 / 148 (7.43%)	28 / 405 (6.91%)
occurrences (all)	22	13	35
Pharyngitis			
subjects affected / exposed	15 / 257 (5.84%)	9 / 148 (6.08%)	24 / 405 (5.93%)
occurrences (all)	19	11	30
Urinary tract infection			
subjects affected / exposed	14 / 257 (5.45%)	9 / 148 (6.08%)	23 / 405 (5.68%)
occurrences (all)	17	13	30
Influenza			
subjects affected / exposed	8 / 257 (3.11%)	10 / 148 (6.76%)	18 / 405 (4.44%)
occurrences (all)	12	17	29
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	6 / 257 (2.33%)	9 / 148 (6.08%)	15 / 405 (3.70%)
occurrences (all)	6	9	15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2015	Main reasons for the second protocol amendment: • The exclusion criterion on laboratory abnormalities had been updated to ensure more consistency between the discontinuation criteria in the preceding Phase llb studies with ALX-0061 (ALX0061-C201 or ALX0061-C202) and the entry criteria of this open-label extension study (ALX0061-C203) and to allow unscheduled lab testing for study entry. • It had been clarified that the term baseline mentioned in the analysis endpoints was referring to the baseline value of the preceding Phase llb study with ALX-0061 (ALX0061-C201 or ALX0061-C202) the subject was enrolled in. • The use of the allowed medication non-steroidal anti-inflammatory drugs (NDAIDs) had been further clarified and the prohibited medications high-potency opioid analgesics had been specified. • It has been specified that additional pregnancy testing is allowed according to local guidelines; however, this additional pregnancy testing is not part of and cannot replace the protocol specific procedures. • Wording with regard to follow-up of adverse events (AEs) was updated to clarify that all AEs were to be followed until satisfactory outcome. • No subgroup analysis by site for efficacy were to be done as the number of patients per site was too limited. • Shift tables on vital signs variables according to their normal ranges were not be created as these were not expected to provide additional clinically useful information on top of the planned descriptive summaries on actual values and changes from baseline of the vital signs parameters; the latter being more relevant in the study population of moderate to severe RA patients. Medical assessment of the values was performed by the Investigator and during the medical review process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported