



## 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 |
|-----------------------|--------------|

##### 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:

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**Results analysis stage**

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|                                                      |                 |
|------------------------------------------------------|-----------------|
| 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:

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**General information about the trial**

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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).

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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.

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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.

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                                                |
|--------------------------------------|------------------------------------------------|
| 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                                     |

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|                                      |                   |
|--------------------------------------|-------------------|
| 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:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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                      |
| <b>Arm title</b>             | 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.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | ALX-0061 150 mg q4w + MTX |
|------------------|---------------------------|

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.                                                                                             |                           |
| <b>Arm title</b>                                                                                                                                                                     | 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.                                                                                             |                           |
| <b>Arm title</b>                                                                                                                                                                     | 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.                                                                                    |                           |
| <b>Arm title</b>                                                                                                                                                                     | 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.                                                                                             |                           |

| <b>Number of subjects in period 1</b> | ALX-0061 75 mg<br>q4w + MTX | ALX-0061 150 mg<br>q4w + MTX | ALX-0061 150 mg<br>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                            | -                            |

| <b>Number of subjects in period 1</b> | ALX-0061 225 mg<br>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:<br>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:<br>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:<br>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:<br>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:<br>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<br>Units: Subjects    |                          |                           |                           |
| Adults (18-64 years)                  | 59                       | 59                        | 56                        |
| From 65-84 years                      | 10                       | 11                        | 12                        |
| Age continuous<br>Units: years        |                          |                           |                           |
| arithmetic mean                       | 53.3                     | 52                        | 51.9                      |
| standard deviation                    | ± 10.35                  | ± 13.16                   | ± 11.93                   |
| Gender categorical<br>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<br>Units: Subjects |                           |                   |       |
| Adults (18-64 years)               | 55                        | 56                | 285   |
| From 65-84 years                   | 14                        | 13                | 60    |
| Age continuous<br>Units: years     |                           |                   |       |
| arithmetic mean                    | 52.3                      | 52.8              | -     |
| standard deviation                 | ± 13.36                   | ± 11.92           | -     |

|                                       |    |    |     |
|---------------------------------------|----|----|-----|
| Gender categorical<br>Units: Subjects |    |    |     |
| Female                                | 55 | 55 | 289 |
| Male                                  | 14 | 14 | 56  |

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### 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

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

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## End points

### End points reporting groups

|                                                                                                                                                                                                                      |                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Reporting group title                                                                                                                                                                                                | ALX-0061 75 mg q4w + MTX  |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 <sup>[1]</sup>        | 70 <sup>[2]</sup>         | 68 <sup>[3]</sup>         | 69 <sup>[4]</sup>         |
| 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

|                             |                   |  |  |  |
|-----------------------------|-------------------|--|--|--|
| <b>End point values</b>     | Placebo q2w + MTX |  |  |  |
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 69 <sup>[5]</sup> |  |  |  |
| Units: percent responders   | 62                |  |  |  |

Notes:

[5] - Intent-to-treat population

## Statistical analyses

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Cochran Armitage Test for Trend |
|-----------------------------------|---------------------------------|

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 <sup>[6]</sup>                                                                                                             |
| 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 |
|-----------------|-------------------------------------------------------|

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 |
|----------------|-----------|

End point timeframe:

at Week 24 visit

|                             |                          |                           |                           |                           |
|-----------------------------|--------------------------|---------------------------|---------------------------|---------------------------|
| <b>End point values</b>     | 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 <sup>[7]</sup>        | 70 <sup>[8]</sup>         | 68 <sup>[9]</sup>         | 69 <sup>[10]</sup>        |
| 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

|                         |                   |  |  |  |
|-------------------------|-------------------|--|--|--|
| <b>End point values</b> | Placebo q2w + MTX |  |  |  |
|-------------------------|-------------------|--|--|--|

|                             |                    |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 69 <sup>[11]</sup> |  |  |  |
| 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:<br>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:<br>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 <sup>[12]</sup>       | 70 <sup>[13]</sup>        | 68 <sup>[14]</sup>        | 69 <sup>[15]</sup>        |
| 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 <sup>[16]</sup> |  |  |  |
| 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 |
|-----------------|---------------------------------------------------------------|

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 <sup>[17]</sup>       | 70 <sup>[18]</sup>        | 68 <sup>[19]</sup>        | 69 <sup>[20]</sup>        |
| 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 <sup>[21]</sup> |  |  |  |
| 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 <sup>[22]</sup>       | 70 <sup>[23]</sup>        | 68 <sup>[24]</sup>        | 69 <sup>[25]</sup>        |
| 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 <sup>[26]</sup> |  |  |  |
| 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) |
|-----------------|----------------------------------------------------------------------------------------|

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 <sup>[27]</sup>       | 70 <sup>[28]</sup>        | 68 <sup>[29]</sup>        | 69 <sup>[30]</sup>        |
| 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

|                             |                    |  |  |  |
|-----------------------------|--------------------|--|--|--|
| <b>End point values</b>     | Placebo q2w + MTX  |  |  |  |
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 69 <sup>[31]</sup> |  |  |  |
| 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:<br>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:<br>at Week 12 and Week 24 visits                                                                                                                                                                                                             |                                                                                |

|                             |                          |                           |                           |                           |
|-----------------------------|--------------------------|---------------------------|---------------------------|---------------------------|
| <b>End point values</b>     | 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 <sup>[32]</sup>       | 70 <sup>[33]</sup>        | 68 <sup>[34]</sup>        | 69 <sup>[35]</sup>        |
| 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

|                             |                    |  |  |  |
|-----------------------------|--------------------|--|--|--|
| <b>End point values</b>     | Placebo q2w + MTX  |  |  |  |
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 69 <sup>[36]</sup> |  |  |  |
| 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) |
|-----------------|------------------------------------------------------------------------------|

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 <sup>[37]</sup>       | 70 <sup>[38]</sup>        | 68 <sup>[39]</sup>        | 69 <sup>[40]</sup>        |
| 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 <sup>[41]</sup> |  |  |  |
| 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:<br>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:<br>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 <sup>[42]</sup>       | 70 <sup>[43]</sup>        | 68 <sup>[44]</sup>        | 69 <sup>[45]</sup>        |
| 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 <sup>[46]</sup> |  |  |  |
| 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:<br>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:<br>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 <sup>[47]</sup>       | 70 <sup>[48]</sup>        | 68 <sup>[49]</sup>        | 69 <sup>[50]</sup>        |
| 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 <sup>[51]</sup> |  |  |  |
| 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 <sup>[52]</sup>       | 70 <sup>[53]</sup>        | 68 <sup>[54]</sup>        | 69 <sup>[55]</sup>        |
| 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 + |  |  |  |
|------------------|---------------|--|--|--|
|------------------|---------------|--|--|--|

|                             | MTX                |  |  |  |
|-----------------------------|--------------------|--|--|--|
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 69 <sup>[56]</sup> |  |  |  |
| 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 <sup>[57]</sup>       | 70 <sup>[58]</sup>        | 68 <sup>[59]</sup>        | 69 <sup>[60]</sup>        |
| 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 <sup>[61]</sup> |  |  |  |
| 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:<br>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:<br>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 <sup>[62]</sup>       | 70 <sup>[63]</sup>        | 68 <sup>[64]</sup>        | 69 <sup>[65]</sup>        |
| 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 <sup>[66]</sup> |  |  |  |
| 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:<br>Missing values were imputed with the last non-missing observation (i.e., LOCF imputation). |                                                                                   |
| End point type                                                                                                       | Secondary                                                                         |
| End point timeframe:<br>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 <sup>[67]</sup>       | 68 <sup>[68]</sup>        | 64 <sup>[69]</sup>        | 67 <sup>[70]</sup>        |
| 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 <sup>[71]</sup> |  |  |  |
| 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) |
| End point description:                             |                                                                                      |
| End point type                                     | Secondary                                                                            |
| End point timeframe:<br>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 <sup>[72]</sup>       | 66 <sup>[73]</sup>        | 58 <sup>[74]</sup>        | 60 <sup>[75]</sup>        |
| 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 <sup>[76]</sup> |  |  |  |
| 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 <sup>[77]</sup>       | 66 <sup>[78]</sup>        | 58 <sup>[79]</sup>        | 60 <sup>[80]</sup>        |
| Units: not applicable            |                          |                           |                           |                           |
| arithmetic mean (standard error) |                          |                           |                           |                           |

|         |                     |                     |                      |                     |
|---------|---------------------|---------------------|----------------------|---------------------|
| Week 12 | 9.096 (±<br>1.4966) | 7.249 (±<br>1.1237) | 9.749 (±<br>1.4177)  | 5.686 (±<br>1.6485) |
| Week 24 | 9.857 (±<br>1.5326) | 7.962 (±<br>1.3932) | 11.739 (±<br>1.4159) | 8.981 (±<br>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)

|                                  |                      |  |  |  |
|----------------------------------|----------------------|--|--|--|
| <b>End point values</b>          | Placebo q2w +<br>MTX |  |  |  |
| Subject group type               | Reporting group      |  |  |  |
| Number of subjects analysed      | 60 <sup>[81]</sup>   |  |  |  |
| Units: not applicable            |                      |  |  |  |
| arithmetic mean (standard error) |                      |  |  |  |
| Week 12                          | 5.569 (±<br>1.6467)  |  |  |  |
| Week 24                          | 6.198 (±<br>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:<br>from baseline till Week 24 |                                                                                                       |

|                                  |                             |                              |                              |                              |
|----------------------------------|-----------------------------|------------------------------|------------------------------|------------------------------|
| <b>End point values</b>          | ALX-0061 75<br>mg q4w + MTX | ALX-0061 150<br>mg q4w + MTX | ALX-0061 150<br>mg q2w + MTX | ALX-0061 225<br>mg q2w + MTX |
| Subject group type               | Reporting group             | Reporting group              | Reporting group              | Reporting group              |
| Number of subjects analysed      | 61 <sup>[82]</sup>          | 65 <sup>[83]</sup>           | 58 <sup>[84]</sup>           | 61 <sup>[85]</sup>           |
| Units: not applicable            |                             |                              |                              |                              |
| arithmetic mean (standard error) |                             |                              |                              |                              |
| Week 12                          | 11.014 (±<br>1.3593)        | 8.63 (±<br>1.0465)           | 10.884 (±<br>1.5424)         | 9.389 (±<br>1.3706)          |
| Week 24                          | 12.446 (±<br>1.5687)        | 10.439 (±<br>1.2157)         | 13.374 (±<br>1.5621)         | 12.381 (±<br>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 <sup>[86]</sup> |  |  |  |
| 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 <sup>[87]</sup> |
|-----------------|-------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 <sup>[88]</sup>       | 70 <sup>[89]</sup>        | 68 <sup>[90]</sup>        | 69 <sup>[91]</sup>        |
| 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) |
|-----------------|-----------------------------------------------------------------------------|

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 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 <sup>[92]</sup>       | 70 <sup>[93]</sup>        | 68 <sup>[94]</sup>        | 69 <sup>[95]</sup>        |
| 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 <sup>[96]</sup> |  |  |  |
| 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 |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
from baseline till follow-up

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

Notes:

[97] - Safety population

[98] - Safety population

[99] - Safety population

[100] - Safety population

| End point values            | Placebo q2w +<br>MTX | ALX-0061 total       |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Reporting group      | Subject analysis set |  |  |
| Number of subjects analysed | 69 <sup>[101]</sup>  | 276 <sup>[102]</sup> |  |  |
| 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)<br>by severity |
|-----------------|----------------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from baseline till Week 24 or Early Termination Visit

| End point values            | ALX-0061 75<br>mg q4w + MTX | ALX-0061 150<br>mg q4w + MTX | ALX-0061 150<br>mg q2w + MTX | ALX-0061 225<br>mg q2w + MTX |
|-----------------------------|-----------------------------|------------------------------|------------------------------|------------------------------|
| Subject group type          | Reporting group             | Reporting group              | Reporting group              | Reporting group              |
| Number of subjects analysed | 69 <sup>[103]</sup>         | 70 <sup>[104]</sup>          | 68 <sup>[105]</sup>          | 69 <sup>[106]</sup>          |
| 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

|                             |                     |  |  |  |
|-----------------------------|---------------------|--|--|--|
| <b>End point values</b>     | Placebo q2w + MTX   |  |  |  |
| Subject group type          | Reporting group     |  |  |  |
| Number of subjects analysed | 69 <sup>[107]</sup> |  |  |  |
| 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 |
|-----------------|---------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from baseline till Week 24 or the Early Termination visit

|                             |                          |                           |                           |                           |
|-----------------------------|--------------------------|---------------------------|---------------------------|---------------------------|
| <b>End point values</b>     | 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 <sup>[108]</sup>      | 70 <sup>[109]</sup>       | 68 <sup>[110]</sup>       | 69 <sup>[111]</sup>       |
| 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

|                             |                     |  |  |  |
|-----------------------------|---------------------|--|--|--|
| <b>End point values</b>     | Placebo q2w + MTX   |  |  |  |
| Subject group type          | Reporting group     |  |  |  |
| Number of subjects analysed | 69 <sup>[112]</sup> |  |  |  |
| Units: Events               |                     |  |  |  |
| mild                        | 49                  |  |  |  |
| moderate                    | 22                  |  |  |  |

|        |   |  |  |  |
|--------|---|--|--|--|
| severe | 2 |  |  |  |
|--------|---|--|--|--|

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) |
|-----------------|-------------------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 <sup>[113]</sup>      | 70 <sup>[114]</sup>       | 68 <sup>[115]</sup>       | 69 <sup>[116]</sup>       |
| 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 <sup>[117]</sup> |  |  |  |
| 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 |
|-----------------|---------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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

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

Notes:

[118] - Safety population

[119] - Safety population

[120] - Safety population

[121] - Safety population

| End point values            | Placebo q2w +<br>MTX |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Reporting group      |  |  |  |
| Number of subjects analysed | 69 <sup>[122]</sup>  |  |  |  |
| 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 |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18     |

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | ALX-0061 75 mg q4w + MTX |
|-----------------------|--------------------------|

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 |
|-----------------------|---------------------------|

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 |
|-----------------------|---------------------------|

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 |
|-----------------------|---------------------------|

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 |
|-----------------------|-------------------|

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          |

| <b>Serious adverse events</b>                                       | ALX-0061 225 mg<br>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 %

| <b>Non-serious adverse events</b>                     | ALX-0061 75 mg<br>q4w + MTX | ALX-0061 150 mg<br>q4w + MTX | ALX-0061 150 mg<br>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<br>subjects affected / exposed<br>occurrences (all)                                                                       | 3 / 69 (4.35%)<br>3 | 2 / 70 (2.86%)<br>2  | 3 / 68 (4.41%)<br>3  |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)                                | 4 / 69 (5.80%)<br>7 | 2 / 70 (2.86%)<br>2  | 0 / 68 (0.00%)<br>0  |
| General disorders and administration<br>site conditions<br>Injection site erythema<br>subjects affected / exposed<br>occurrences (all) | 4 / 69 (5.80%)<br>5 | 5 / 70 (7.14%)<br>7  | 7 / 68 (10.29%)<br>8 |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                          | 6 / 69 (8.70%)<br>7 | 2 / 70 (2.86%)<br>2  | 3 / 68 (4.41%)<br>3  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                                                    | 4 / 69 (5.80%)<br>4 | 5 / 70 (7.14%)<br>5  | 2 / 68 (2.94%)<br>2  |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                                                                        | 2 / 69 (2.90%)<br>2 | 6 / 70 (8.57%)<br>6  | 3 / 68 (4.41%)<br>4  |
| Metabolism and nutrition disorders<br>Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 69 (2.90%)<br>2 | 7 / 70 (10.00%)<br>7 | 4 / 68 (5.88%)<br>6  |

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

|                                                                                                                                                                                                                                                 |                                                                           |                                                                           |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|--|
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                | 4 / 69 (5.80%)<br>5                                                       | 1 / 69 (1.45%)<br>1                                                       |  |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                         | 0 / 69 (0.00%)<br>0                                                       | 0 / 69 (0.00%)<br>0                                                       |  |
| General disorders and administration<br>site conditions<br>Injection site erythema<br>subjects affected / exposed<br>occurrences (all)                                                                                                          | 3 / 69 (4.35%)<br>3                                                       | 0 / 69 (0.00%)<br>0                                                       |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Pharyngitis<br>subjects affected / exposed<br>occurrences (all) | 3 / 69 (4.35%)<br>3<br><br>4 / 69 (5.80%)<br>4<br><br>1 / 69 (1.45%)<br>1 | 3 / 69 (4.35%)<br>3<br><br>6 / 69 (8.70%)<br>6<br><br>0 / 69 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders<br>Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                 | 5 / 69 (7.25%)<br>6                                                       | 4 / 69 (5.80%)<br>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"><li>• 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.</li><li>• Inclusion criterion on active RA was updated to allow inclusion of subjects with C-reactive protein (CRP) &gt; 1.0 × upper limit of normal (ULN) at screening.</li><li>• 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.</li><li>• Pregnancy testing was clarified to confirm that it applied only to women of childbearing potential.</li><li>• 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).</li><li>• 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.</li><li>• High-potency opioid analgesics were specified as prohibited medication during subjects' participation in the study.</li><li>• The Investigator was directed to refer to the CTCAE v4.0 criteria to assess the severity of adverse events (AEs) related to laboratory abnormalities.</li></ul> |

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: