



## Clinical trial results:

### A Multicenter, Randomized, Double-Blind, Active and Placebo-Controlled 16 Week Study Followed by Long Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Radiographic Axial Spondyloarthritis.

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2015-003932-11  |
| Trial protocol           | DE HU PL NL CZ  |
| Global end of trial date | 17 October 2018 |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 29 December 2019  |
| First version publication date | 10 October 2019   |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Correction of full data set |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | I1F-MC-RHBV |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                     |
|------------------------------------|---------------------|
| ISRCTN number                      | -                   |
| ClinicalTrials.gov id (NCT number) | NCT02696785         |
| WHO universal trial number (UTN)   | -                   |
| Other trial identifiers            | Trial Number: 16178 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Eli Lilly and Company   |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285            |
| Public contact               | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559, |

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**

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 17 October 2018 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 17 October 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

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**General information about the trial**

Main objective of the trial:

The main purpose of this study is to evaluate the safety and efficacy of the study drug known as ixekizumab in biological disease-modifying anti-rheumatic drugs (bDMARDs)-naïve participants with radiographic axial spondyloarthritis (rad-axSpA).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 02 May 2016 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 47 |
| Country: Number of subjects enrolled | Netherlands: 4         |
| Country: Number of subjects enrolled | United States: 15      |
| Country: Number of subjects enrolled | Japan: 7               |
| Country: Number of subjects enrolled | Taiwan: 51             |
| Country: Number of subjects enrolled | Germany: 3             |
| Country: Number of subjects enrolled | Canada: 9              |
| Country: Number of subjects enrolled | Hungary: 10            |
| Country: Number of subjects enrolled | Mexico: 30             |
| Country: Number of subjects enrolled | Poland: 62             |
| Country: Number of subjects enrolled | Russian Federation: 48 |
| Country: Number of subjects enrolled | Czech Republic: 54     |
| Worldwide total number of subjects   | 340                    |
| EEA total number of subjects         | 133                    |

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)                      | 326 |
| From 65 to 84 years                       | 14  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Blinded treatment period (Week 0 to Week 16), followed by extended treatment period (Week 16 to Week 52), followed by post treatment period for a maximum of 24 weeks.

Washout period occurred for only Adalimumab group for 6 weeks (Week 14 to Week 20).

### Pre-assignment

Screening details:

Participants who completed study were eligible to enroll into a long-term study (Study I1F-MC-RHBY [RHBY]) for up to 2 additional years. Participants that do not enroll into study RHBY will complete the Post-Treatment Follow-Up Period.

### Period 1

|                              |                          |
|------------------------------|--------------------------|
| Period 1 title               | Blinded Treatment 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>             | Placebo (PBO) |

Arm description:

Participants received placebo every two weeks by subcutaneous injection.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Placebo          |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Participants received placebo by subcutaneous injection.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Adalimumab |
|------------------|------------|

Arm description:

Blinded Treatment Period: Participants received 40mg Adalimumab every two weeks by SC injection.

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Adalimumab        |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Subcutaneous use  |

Dosage and administration details:

Participants received 40mg Adalimumab by subcutaneous injection every two weeks.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | IXE80Q2W |
|------------------|----------|

Arm description:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                  |
|--|------------------|
| Investigational medicinal product name | Ixekizumab       |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | IXE80Q4W |
|------------------|----------|

Arm description:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks by subcutaneous injection.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Ixekizumab       |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks by subcutaneous injection.

| <b>Number of subjects in period 1</b>    | Placebo (PBO) | Adalimumab | IXE80Q2W |
|--|---------------|------------|----------|
| Started                                  | 86            | 90         | 83       |
| Received at least one dose of study drug | 86            | 90         | 83       |
| Completed                                | 86            | 88         | 79       |
| Not completed                            | 0             | 2          | 4        |
| Consent withdrawn by subject             | -             | 1          | 1        |
| Adverse event, non-fatal                 | -             | 1          | 3        |
| Lack of efficacy                         | -             | -          | -        |

| <b>Number of subjects in period 1</b>    | IXE80Q4W |
|--|----------|
| Started                                  | 81       |
| Received at least one dose of study drug | 81       |
| Completed                                | 78       |
| Not completed                            | 3        |
| Consent withdrawn by subject             | 2        |
| Adverse event, non-fatal                 | -        |
| Lack of efficacy                         | 1        |

**Period 2**

|                              |                           |
|------------------------------|---------------------------|
| Period 2 title               | Extended Treatment Period |
| Is this the baseline period? | No                        |
| Allocation method            | Randomised - controlled   |
| Blinding used                | Double blind              |
| Roles blinded                | Subject, Investigator     |

**Arms**

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |         |
|------------------|---------|
| <b>Arm title</b> | PBO/IXE |
|------------------|---------|

## Arm description:

Participants received starting dose of 160mg Ixekizumab at week 16 followed by 80mg Ixekizumab either every two weeks (Q2W) or every four weeks (Q4W) by subcutaneous (SC) injection.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Ixekizumab       |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

## Dosage and administration details:

Participants received starting dose of 160mg Ixekizumab at week 16 followed by 80mg Ixekizumab either every two weeks (Q2W) or every four weeks (Q4W) by subcutaneous (SC) injection during extended treatment period.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Adalimumab/PBO/IXE |
|------------------|--------------------|

## Arm description:

Participants who received Adalimumab in blinded treatment period received 80mg Ixekizumab either Q2W or Q4W by SC injection during extension treatment period.

Washout Period: Participants received placebo for 6 weeks.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Ixekizumab       |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

## Dosage and administration details:

Participants received 80mg Ixekizumab either Q2W or Q4W by SC injection.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | IXE80Q2W/IXE80Q2W |
|------------------|-------------------|

## Arm description:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Ixekizumab       |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

## Dosage and administration details:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | IXE80Q4W/IXE80Q4W |
|------------------|-------------------|

## Arm description:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks by subcutaneous injection.

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Ixekizumab       |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

**Dosage and administration details:**

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | PBO/IXE | Adalimumab/PBO/IXE | IXE80Q2W/IXE80Q2W |
|---|---------|--------------------|-------------------|
| Started   | 86      | 86                 | 79                |
| Completed   | 83      | 80                 | 74                |
| Not completed                                       | 3       | 6                  | 5                 |
| Consent withdrawn by subject                        | 1       | 2                  | 3                 |
| Adverse event, non-fatal                            | 2       | 3                  | 2                 |
| Lack of efficacy                                    | -       | 1                  | -                 |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | IXE80Q4W/IXE80Q4W |
|---|-------------------|
| Started   | 78                |
| Completed   | 72                |
| Not completed                                       | 6                 |
| Consent withdrawn by subject                        | 5                 |
| Adverse event, non-fatal                            | 1                 |
| Lack of efficacy                                    | -                 |

**Notes:**

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Adalimumab group has two participants in the washout period discontinuing the study. 1 participant with Lack of efficacy, 1 participant with consent withdrawn by subject.

**Period 3**

|                              |                  |
|------------------------------|------------------|
| Period 3 title               | Follow-up Period |
| Is this the baseline period? | No               |
| Allocation method            | Not applicable   |
| Blinding used                | Not blinded      |

**Arms**

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|  |                 |
|--|-----------------|
| <b>Arm title</b>   | Placebo (PBO)   |
| Arm description:<br>Participants did not receive any intervention during follow-up period. |                 |
| Arm type   | No intervention |
| No investigational medicinal product assigned in this arm                                  |                 |
| <b>Arm title</b>   | IXE80Q2W        |
| Arm description:<br>Participants did not receive any intervention during Follow-up period. |                 |
| Arm type   | No intervention |
| No investigational medicinal product assigned in this arm                                  |                 |
| <b>Arm title</b>   | IXE80Q4W        |
| Arm description:<br>Participants did not receive any intervention during Follow-up period. |                 |
| Arm type   | No intervention |
| No investigational medicinal product assigned in this arm                                  |                 |

| <b>Number of subjects in period 3<sup>[2]</sup></b> | Placebo (PBO) | IXE80Q2W | IXE80Q4W |
|---|---------------|----------|----------|
| Started   | 1             | 24       | 16       |
| Completed   | 0             | 11       | 8        |
| Not completed                                       | 1             | 13       | 8        |
| Consent withdrawn by subject                        | 1             | 5        | 4        |
| Adverse event, non-fatal                            | -             | 8        | 2        |
| Lost to follow-up                                   | -             | -        | 1        |
| Lack of efficacy                                    | -             | -        | 1        |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who completed study were eligible to enroll RHBV directly without entering Follow-Up period.



## Baseline characteristics

### Reporting groups

|  |               |
|--|---------------|
| Reporting group title  | Placebo (PBO) |
| Reporting group description:   |               |
| Participants received placebo every two weeks by subcutaneous injection.   |               |
| Reporting group title  | Adalimumab    |
| Reporting group description:   |               |
| Blinded Treatment Period: Participants received 40mg Adalimumab every two weeks by SC injection.   |               |
| Reporting group title  | IXE80Q2W      |
| Reporting group description:   |               |
| Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.  |               |
| Reporting group title  | IXE80Q4W      |
| Reporting group description:   |               |
| Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks by subcutaneous injection. |               |

| Reporting group values                             | Placebo (PBO) | Adalimumab | IXE80Q2W |
|--|---------------|------------|----------|
| Number of subjects                                 | 86            | 90         | 83       |
| Age categorical                                    |               |            |          |
| Units: Subjects                                    |               |            |          |
| In utero   |               |            |          |
| Preterm newborn infants (gestational age < 37 wks) |               |            |          |
| Newborns (0-27 days)                               |               |            |          |
| Infants and toddlers (28 days-23 months)           |               |            |          |
| Children (2-11 years)                              |               |            |          |
| Adolescents (12-17 years)                          |               |            |          |
| Adults (18-64 years)                               |               |            |          |
| From 65-84 years                                   |               |            |          |
| 85 years and over                                  |               |            |          |
| Age continuous                                     |               |            |          |
| Units: years                                       |               |            |          |
| arithmetic mean                                    | 42.7          | 41.8       | 41.3     |
| standard deviation                                 | ± 12.01       | ± 11.44    | ± 11.17  |
| Gender categorical                                 |               |            |          |
| Units: Subjects                                    |               |            |          |
| Female   | 15            | 17         | 19       |
| Male   | 71            | 73         | 64       |
| Ethnicity (NIH/OMB)                                |               |            |          |
| Units: Subjects                                    |               |            |          |
| Hispanic or Latino                                 | 11            | 7          | 8        |
| Not Hispanic or Latino                             | 67            | 74         | 68       |
| Unknown or Not Reported                            | 8             | 9          | 7        |
| Race (NIH/OMB)                                     |               |            |          |
| Units: Subjects                                    |               |            |          |
| American Indian or Alaska Native                   | 4             | 2          | 4        |

|   |    |    |    |
|---|----|----|----|
| Asian                                     | 28 | 29 | 25 |
| Native Hawaiian or Other Pacific Islander | 0  | 0  | 0  |
| Black or African American                 | 0  | 0  | 0  |
| White                                     | 52 | 57 | 52 |
| More than one race                        | 2  | 2  | 2  |
| Unknown or Not Reported                   | 0  | 0  | 0  |
| Region of Enrollment                      |    |    |    |
| Units: Subjects                           |    |    |    |
| South Korea                               | 10 | 14 | 12 |
| Netherlands                               | 0  | 2  | 2  |
| United States                             | 5  | 3  | 4  |
| Japan                                     | 3  | 3  | 0  |
| Taiwan                                    | 13 | 12 | 13 |
| Germany                                   | 0  | 2  | 1  |
| Canada                                    | 2  | 3  | 2  |
| Hungary                                   | 3  | 2  | 2  |
| Mexico                                    | 8  | 7  | 8  |
| Poland                                    | 16 | 15 | 15 |
| Russia                                    | 12 | 13 | 11 |
| Czech Republic                            | 14 | 14 | 13 |

| Reporting group values                             | IXE80Q4W | Total |  |
|--|----------|-------|--|
| Number of subjects                                 | 81       | 340   |  |
| Age categorical                                    |          |       |  |
| Units: Subjects                                    |          |       |  |
| In utero   |          | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) |          | 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)                               |          | 0     |  |
| From 65-84 years                                   |          | 0     |  |
| 85 years and over                                  |          | 0     |  |
| Age continuous                                     |          |       |  |
| Units: years                                       |          |       |  |
| arithmetic mean                                    | 41.0     |       |  |
| standard deviation                                 | ± 12.13  | -     |  |
| Gender categorical                                 |          |       |  |
| Units: Subjects                                    |          |       |  |
| Female   | 13       | 64    |  |
| Male   | 68       | 276   |  |
| Ethnicity (NIH/OMB)                                |          |       |  |
| Units: Subjects                                    |          |       |  |
| Hispanic or Latino                                 | 8        | 34    |  |
| Not Hispanic or Latino                             | 66       | 275   |  |
| Unknown or Not Reported                            | 7        | 31    |  |
| Race (NIH/OMB)                                     |          |       |  |
| Units: Subjects                                    |          |       |  |

|   |    |     |  |
|---|----|-----|--|
| American Indian or Alaska Native          | 4  | 14  |  |
| Asian                                     | 25 | 107 |  |
| Native Hawaiian or Other Pacific Islander | 0  | 0   |  |
| Black or African American                 | 0  | 0   |  |
| White                                     | 52 | 213 |  |
| More than one race                        | 0  | 6   |  |
| Unknown or Not Reported                   | 0  | 0   |  |
| Region of Enrollment                      |    |     |  |
| Units: Subjects                           |    |     |  |
| South Korea                               | 11 | 47  |  |
| Netherlands                               | 0  | 4   |  |
| United States                             | 3  | 15  |  |
| Japan                                     | 1  | 7   |  |
| Taiwan                                    | 13 | 51  |  |
| Germany                                   | 0  | 3   |  |
| Canada                                    | 2  | 9   |  |
| Hungary                                   | 3  | 10  |  |
| Mexico                                    | 7  | 30  |  |
| Poland                                    | 16 | 62  |  |
| Russia                                    | 12 | 48  |  |
| Czech Republic                            | 13 | 54  |  |

## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | Placebo (PBO)      |
| Reporting group description:<br>Participants received placebo every two weeks by subcutaneous injection.   |                    |
| Reporting group title  | Adalimumab         |
| Reporting group description:<br>Blinded Treatment Period: Participants received 40mg Adalimumab every two weeks by SC injection.   |                    |
| Reporting group title  | IXE80Q2W           |
| Reporting group description:<br>Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.  |                    |
| Reporting group title  | IXE80Q4W           |
| Reporting group description:<br>Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks by subcutaneous injection.   |                    |
| Reporting group title  | PBO/IXE            |
| Reporting group description:<br>Participants received starting dose of 160mg Ixekizumab at week 16 followed by 80mg Ixekizumab either every two weeks (Q2W) or every four weeks (Q4W) by subcutaneous (SC) injection.  |                    |
| Reporting group title  | Adalimumab/PBO/IXE |
| Reporting group description:<br>Participants who received Adalimumab in blinded treatment period received 80mg Ixekizumab either Q2W or Q4W by SC injection during extension treatment period.<br>Washout Period: Participants received placebo for 6 weeks.           |                    |
| Reporting group title  | IXE80Q2W/IXE80Q2W  |
| Reporting group description:<br>Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.  |                    |
| Reporting group title  | IXE80Q4W/IXE80Q4W  |
| Reporting group description:<br>Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks by subcutaneous injection.   |                    |
| Reporting group title  | Placebo (PBO)      |
| Reporting group description:<br>Participants did not receive any intervention during follow-up period.   |                    |
| Reporting group title  | IXE80Q2W           |
| Reporting group description:<br>Participants did not receive any intervention during Follow-up period.   |                    |
| Reporting group title  | IXE80Q4W           |
| Reporting group description:<br>Participants did not receive any intervention during Follow-up period.   |                    |
| Subject analysis set title   | PBO/IXE            |
| Subject analysis set type  | Per protocol       |
| Subject analysis set description:<br>Participants received placebo every two weeks during blinded treatment period and starting dose of 160mg Ixekizumab at week 16 followed by 80mg Ixekizumab either Q2W or Q4W extended treatment period by subcutaneous injection. |                    |
| Subject analysis set title   | Adalimumab/IXE     |
| Subject analysis set type  | Per protocol       |

Subject analysis set description:

Participants received 40mg Adalimumab every two weeks during blinded treatment period and 80mg Ixekizumab either Q2W or Q4W during extended treatment period by subcutaneous injection.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | IXE80Q4W/IXE80Q4W |
| Subject analysis set type  | Per protocol      |

Subject analysis set description:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks during blinded treatment and extension period by subcutaneous injection.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | IXE80Q2W/IXE80Q2W |
| Subject analysis set type  | Per protocol      |

Subject analysis set description:

Participants received starting dose of either 80 milligrams (mg) or 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks during blinded treatment and extension period by subcutaneous injection.

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | IXE160/80Q4W |
| Subject analysis set type  | Per protocol |

Subject analysis set description:

Participants received starting dose of 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks by subcutaneous injection.

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | IXE160/80Q2W |
| Subject analysis set type  | Per protocol |

Subject analysis set description:

Participants received starting dose of 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every two weeks by subcutaneous injection.

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### **Primary: Percentage of Participants Achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) Response**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants Achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) Response |
|-----------------|--|

End point description:

ASAS40 is defined as improvement from baseline of greater than or equal to ( $\geq$ ) 40% and absolute improvement from baseline of at least 2 units in at least 3 of the following 4 domains without any worsening in the remaining domains.

- 1.Patient Global: How active was your spondylitis on average during the last week? score range 0 (not active) to 10 (very active).
- 2.Spinal Pain: How much Pain of your spine due to Ankylosing spondylitis? score ranges 0 (no pain) to 10 (severe pain).
- 3.Bath Ankylosing Spondylitis Functional Index: Participant is asked to rate the difficulty associated with 10 individual basic functional activities. Participants response is captured using NRS scale (range 0 to 10) with a higher score indicating worse function.
- 4.Inflammation based on Q5 & Q6 mean of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (mean of intensity & duration of stiffness): Score ranges from "0" (none) and "10" (very severe).

APD: All Randomized Participants.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 16

| End point values                  | Placebo (PBO)     | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-----------------------------------|-------------------|-----------------|-----------------|-----------------|
| Subject group type                | Reporting group   | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed       | 86 <sup>[1]</sup> | 90              | 83              | 81              |
| Units: percentage of participants |                   |                 |                 |                 |
| number (not applicable)           | 18.4              | 35.6            | 51.8            | 48.1            |

Notes:

[1] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

| Statistical analysis title              | Statistical Analysis 1     |
|---|----------------------------|
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 176                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| P-value                                 | = 0.005                    |
| Method                                  | Regression, Logistic       |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 2.73                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.35                       |
| upper limit                             | 5.52                       |

Notes:

[2] - Total participants 177. one participant who did not receive study drug is included in the analysis.

| Statistical analysis title              | Statistical Analysis 2     |
|---|----------------------------|
| Comparison groups                       | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis | 167                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Regression, Logistic       |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 4.45                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 2.2                        |
| upper limit                             | 9.03                       |

Notes:

[3] - Total participants 168. one participant who did not receive study drug is included in the analysis.

| Statistical analysis title | Statistical Analysis 3   |
|----------------------------|--------------------------|
| Comparison groups          | Placebo (PBO) v IXE80Q2W |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 169                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[4]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Regression, Logistic       |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 5.09                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 2.52                       |
| upper limit                             | 10.28                      |

Notes:

[4] - Total participants 170. one participant who did not receive study drug is included in the analysis.

## Secondary: Percentage of Participants Achieving an ASAS20 Response

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Achieving an ASAS20 Response |
|-----------------|---|

End point description:

ASAS20 response is defined as a  $\geq 20\%$  improvement and an absolute improvement from baseline of  $\geq 1$  units in  $\geq 3$  of 4 following domains and no worsening of  $\geq 20\%$  and  $\geq 1$  unit (range 0 to 10) in the remaining domain.

- 1.Patient Global: How active was your spondylitis on average during the last week? score range 0 (not active) to 10 (very active).
- 2.Spinal Pain: How much Pain of your spine due to Ankylosing spondylitis? score ranges 0 (no pain) to 10 (severe pain).
- 3.Bath Ankylosing Spondylitis Functional Index: Participant is asked to rate the difficulty associated with 10 individual basic functional activities. Participants response is captured using NRS scale (range 0 to 10) with a higher score indicating worse function.
- 4.Inflammation based on Q5 & Q6 mean of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (mean of intensity & duration of stiffness): Score ranges from "0" (none) and "10" (very severe).

Analysis Population Description (APD): All Randomized Participants.

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

End point timeframe:

Week 16

| End point values                  | Placebo (PBO)   | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed       | 86              | 90              | 83              | 81              |
| Units: percentage of participants |                 |                 |                 |                 |
| number (not applicable)           | 40.2            | 58.9            | 68.7            | 64.2            |

## Statistical analyses

|                            |                            |
|----------------------------|----------------------------|
| Statistical analysis title | Statistical Analysis 1     |
| Comparison groups          | Adalimumab v Placebo (PBO) |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 176                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[5]</sup> |
| P-value                                 | = 0.007                    |
| Method                                  | Regression, Logistic       |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 2.3                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.25                       |
| upper limit                             | 4.23                       |

Notes:

[5] - Total participants 177. one participant who did not receive study drug is included in the analysis.

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2     |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis | 167                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[6]</sup> |
| P-value                                 | = 0.001                    |
| Method                                  | Regression, Logistic       |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 2.78                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.48                       |
| upper limit                             | 5.24                       |

Notes:

[6] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3     |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W   |
| Number of subjects included in analysis | 169                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[7]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Regression, Logistic       |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 3.39                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.79                       |
| upper limit                             | 6.41                       |

Notes:

[7] - Total participants 170. one participant who did not receive study drug is included in the analysis.

---

## Secondary: Change from Baseline in Ankylosing Spondylitis Disease Activity Score

---



**(ASDAS)**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) |
|-----------------|---|

End point description:

ASDAS is a composite index to assess disease activity in AS. The parameters used for the ASDAS (with CRP as acute phase reactant) are the following:

- 1.Total back pain
- 2.Patient global
- 3.Peripheral pain/swelling
- 4.Duration of morning stiffness
- 5.CRP in mg/L The ASDAScrp is calculated with the following equation:  $0.121 \times \text{total back pain} + 0.110 \times \text{patient global} + 0.073 \times \text{peripheral pain/swelling} + 0.058 \times \text{duration of morning stiffness} + 0.579 \times \ln(\text{CRP}+1)$ . CRP is in mg/liter, the range of other variables is from 0 to 10. Data from five variables combined to yield a score (0.6361 to no defined upper limit), where higher scores indicated higher disease activity. Ln represents the natural logarithm.

Least Square (LS) Mean was calculated using mixed model repeated measures (MMRM) model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 16    |           |

| End point values                    | Placebo (PBO)     | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-------------------------------------|-------------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group   | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 86 <sup>[8]</sup> | 90              | 83              | 81              |
| Units: score on a scale             |                   |                 |                 |                 |
| least squares mean (standard error) | -0.46 (± 0.099)   | -1.30 (± 0.096) | -1.37 (± 0.101) | -1.43 (± 0.102) |

Notes:

[8] - Total participants 87, one participant who did not receive study drug is included in the analysis.

**Statistical analyses**

|   |                            |
|---|----------------------------|
| Statistical analysis title              | Statistical Analysis 1     |
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 176                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[9]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.84                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.11                      |
| upper limit                             | -0.57                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.137                      |

Notes:

[9] - Total participants 177. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2      |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[10]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.97                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.25                       |
| upper limit                             | -0.7                        |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.141                       |

Notes:

[10] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[11]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.91                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.18                       |
| upper limit                             | -0.63                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.14                        |

Notes:

[11] - Total participants 170. one participant who did not receive study drug is included in the analysis.

## **Secondary: Percentage of Participants Achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) Response**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants Achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) Response |
|-----------------|--|

End point description:

The BASDAI is a participant-reported assessment consisting of 6 questions that relate to 5 major symptoms relevant to radiographic axial spondyloarthritis measuring discomfort, pain, and fatigue. 1) Fatigue, 2) Spinal pain, 3) Peripheral arthritis, 4) Enthesitis, 5) Intensity, and 6) Duration of morning stiffness. participants need to score each item with a score from 0 to 10 (NRS). total score is obtained from the average of symptom scores ranging 0 (no problem) to 10 (worst problem). BASDAI50 represents an improvement of  $\geq 50\%$  of the BASDAI score from baseline.

APD: All Randomized Participants.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 16              |           |

| End point values                  | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-----------------------------------|--------------------|-----------------|-----------------|-----------------|
| Subject group type                | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed       | 86 <sup>[12]</sup> | 90              | 83              | 81              |
| Units: percentage of participants |                    |                 |                 |                 |
| number (not applicable)           | 17.2               | 32.2            | 43.4            | 42.0            |

Notes:

[12] - Total participants 87, one participant who did not receive study drug is included in the analysis.

### Statistical analyses

| Statistical analysis title              | Statistical Analysis 1      |
|---|-----------------------------|
| Comparison groups                       | Placebo (PBO) v Adalimumab  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[13]</sup> |
| P-value                                 | = 0.012                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 2.53                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.23                        |
| upper limit                             | 5.21                        |

Notes:

[13] - Total participants 177. one participant who did not receive study drug is included in the analysis.

| Statistical analysis title              | Statistical Analysis 2      |
|---|-----------------------------|
| Comparison groups                       | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[14]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 3.74                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.82                        |
| upper limit                             | 7.7                         |

Notes:

[14] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[15]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 3.9                         |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.91                        |
| upper limit                             | 7.98                        |

Notes:

[15] - Total participants 170. one participant who did not receive study drug is included in the analysis.

### **Secondary: Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) |
|-----------------|--|

End point description:

The BASFI is a participant-reported assessment that establishes a participants functional baseline and subsequent response to treatment. To complete the BASFI, a participant is asked to rate the difficulty associated with 10 individual basic functional activities. Participants respond to each question using an NRS scale (range 0 to 10) with a higher score indicating worse function. The participants final BASFI score is the mean of the 10 item scores has a possible minimum value of 0 and a possible maximum value of 10, with a higher score indicating worse function.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 16    |           |

|                                     |                    |                 |                 |                 |
|-------------------------------------|--------------------|-----------------|-----------------|-----------------|
| <b>End point values</b>             | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
| Subject group type                  | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 86 <sup>[16]</sup> | 90              | 83              | 81              |
| Units: score on a scale             |                    |                 |                 |                 |
| least squares mean (standard error) | -1.16 (± 0.215)    | -2.14 (± 0.209) | -2.43 (± 0.219) | -2.39 (± 0.222) |

Notes:

[16] - Total participants 87, one participant who did not receive study drug is included in the analysis.

### **Statistical analyses**

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1      |
| Comparison groups                       | Placebo (PBO) v Adalimumab  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[17]</sup> |
| P-value                                 | = 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.97                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.56                       |
| upper limit                             | -0.39                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.299                       |

Notes:

[17] - Total participants 177. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2      |
| Comparison groups                       | IXE80Q4W v Placebo (PBO)    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[18]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -1.22                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.83                       |
| upper limit                             | -0.62                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.307                       |

Notes:

[18] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[19]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -1.27                       |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -1.86                      |
| upper limit          | -0.67                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.304                      |

Notes:

[19] - Total participants 170. one participant who did not receive study drug is included in the analysis.

## Secondary: Percentage of Participants Achieving ASDAS Inactive Disease

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Achieving ASDAS Inactive Disease |
|-----------------|---|

End point description:

ASDAS is a composite index to assess disease activity in AS. The parameters used for the ASDAS (with CRP as acute phase reactant) are the following:

- 1.Total back pain
- 2.Patient global
- 3.Peripheral pain/swelling
- 4.Duration of morning stiffness
- 5.CRP in mg/L The ASDAScrp is calculated with the following equation:  $0.121 \times \text{total back pain} + 0.110 \times \text{patient global} + 0.073 \times \text{peripheral pain/swelling} + 0.058 \times \text{duration of morning stiffness} + 0.579 \times \ln(\text{CRP}+1)$ . CRP is in mg/liter, the range of other variables is from 0 to 10.Data from five variables combined to yield a score (0.6361 to no defined upper limit), where higher scores indicated higher disease activity. Ln represents the natural logarithm. ASDAS Inactive Disease is defined as a score of <1.3.

APD: All Randomized Participants.

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

End point timeframe:

Week 16

| End point values                  | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-----------------------------------|--------------------|-----------------|-----------------|-----------------|
| Subject group type                | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed       | 86 <sup>[20]</sup> | 90              | 83              | 81              |
| Units: percentage of Participants |                    |                 |                 |                 |
| number (not applicable)           | 2.3                | 15.6            | 10.8            | 16.0            |

Notes:

[20] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

|   |                             |
|---|-----------------------------|
| Statistical analysis title              | Statistical Analysis 1      |
| Comparison groups                       | Adalimumab v Placebo (PBO)  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[21]</sup> |
| P-value                                 | = 0.009                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 7.62                        |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 1.67    |
| upper limit         | 34.68   |

Notes:

[21] - Total participants 177. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2      |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[22]</sup> |
| P-value                                 | = 0.007                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 8.03                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.75                        |
| upper limit                             | 36.83                       |

Notes:

[22] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[23]</sup> |
| P-value                                 | = 0.041                     |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 5.13                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.07                        |
| upper limit                             | 24.49                       |

Notes:

[23] - Total participants 170. one participant who did not receive study drug is included in the analysis.

### **Secondary: Change from Baseline in Magnetic Resonance Imaging (MRI) of the Spine (Ankylosing Spondylitis Spinal Magnetic Resonance Imaging [ASSpiMRI] - Berlin Score)**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Magnetic Resonance Imaging (MRI) of the Spine (Ankylosing Spondylitis Spinal Magnetic Resonance Imaging [ASSpiMRI] - Berlin Score) |
|-----------------|--|

End point description:

The Berlin modification of Ankylosing Spondylitis spine MRI score for activity (ASSpMRI) scoring technique assesses inflammation in each of 23 disco-vertebral units (DVU). All 23 disco-vertebral units

(DVU) of the spine (from C2 to S1) are scored for bone marrow edema. Scores for each DVU range from 0-3 (0=normal; 1=minor bone marrow edema [less than or equal to 25% of DVU; 3=severe bone marrow edema (more than 50% of DVU)]. The composite score ranges from 0 to 69, with higher scores reflecting worse disease.

LSMean was calculated using ANCOVA model with treatment, geographic region, baseline CRP status and baseline value as fixed factors.

APD: All Randomized Participants with baseline and week 16 Berlin score.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 16    |           |

| End point values                    | Placebo (PBO)        | Adalimumab           | IXE80Q2W             | IXE80Q4W             |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed         | 81                   | 82                   | 76                   | 78                   |
| Units: score on a scale             |                      |                      |                      |                      |
| least squares mean (standard error) | -0.15 ( $\pm$ 0.323) | -2.92 ( $\pm$ 0.314) | -2.54 ( $\pm$ 0.330) | -2.77 ( $\pm$ 0.328) |

## Statistical analyses

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1     |
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 163                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -2.78                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -3.7                       |
| upper limit                             | -1.9                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.447                      |

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2   |
| Comparison groups                 | Placebo (PBO) v IXE80Q4W |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 159                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -2.62                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -3.5                       |
| upper limit                             | -1.7                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.45                       |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3     |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W   |
| Number of subjects included in analysis | 157                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -2.39                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -3.3                       |
| upper limit                             | -1.5                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.452                      |

## **Secondary: Change from Baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores |
|-----------------|---|

### **End point description:**

The SF-36 is a 36-item participant administered measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role – physical, role – emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 overarching domains of mental well-being and physical well-being are captured by the Mental Component Summary and Physical Component Summary scores. T-scores are used for analysis. The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

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

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)      | Adalimumab        | IXE80Q2W          | IXE80Q4W          |
|-------------------------------------|--------------------|-------------------|-------------------|-------------------|
| Subject group type                  | Reporting group    | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed         | 86 <sup>[24]</sup> | 90                | 83                | 81                |
| Units: score on a scale             |                    |                   |                   |                   |
| least squares mean (standard error) |                    |                   |                   |                   |
| PCS                                 | 3.6432 (± 0.7530)  | 6.9005 (± 0.7310) | 7.9686 (± 0.7665) | 7.6952 (± 0.7768) |
| MCS                                 | 2.1229 (± 0.8431)  | 2.5550 (± 0.8225) | 2.5696 (± 0.8650) | 2.7502 (± 0.8763) |

Notes:

[24] - Total participants 87, one participant who did not receive study drug is included in the analysis.

### Statistical analyses

| Statistical analysis title              | Statistical Analysis 1      |
|---|-----------------------------|
| Statistical analysis description:       |                             |
| PCS                                     |                             |
| Comparison groups                       | Placebo (PBO) v Adalimumab  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[25]</sup> |
| P-value                                 | = 0.002                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | 3.2574                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.2041                      |
| upper limit                             | 5.3106                      |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 1.0437                      |

Notes:

[25] - Total participants 177. one participant who did not receive study drug is included in the analysis.

| Statistical analysis title        | Statistical Analysis 2   |
|-----------------------------------|--------------------------|
| Statistical analysis description: |                          |
| PCS                               |                          |
| Comparison groups                 | Placebo (PBO) v IXE80Q4W |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[26]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | 4.052                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.9432                      |
| upper limit                             | 6.1608                      |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 1.072                       |

Notes:

[26] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Statistical analysis description:       |                             |
| PCS                                     |                             |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[27]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | 4.3254                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 2.2321                      |
| upper limit                             | 6.4186                      |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 1.0641                      |

Notes:

[27] - Total participants 170. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 4      |
| Statistical analysis description:       |                             |
| MCS                                     |                             |
| Comparison groups                       | Placebo (PBO) v Adalimumab  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[28]</sup> |
| P-value                                 | = 0.713                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | 0.4321                      |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -1.8732                    |
| upper limit          | 2.7373                     |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 1.1718                     |

Notes:

[28] - Total participants 177. one participant who did not receive study drug is included in the analysis.

|  |                             |
|--|-----------------------------|
| <b>Statistical analysis title</b>        | Statistical Analysis 5      |
| Statistical analysis description:<br>MCS |                             |
| Comparison groups                        | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis  | 167                         |
| Analysis specification                   | Pre-specified               |
| Analysis type                            | superiority <sup>[29]</sup> |
| P-value                                  | = 0.602                     |
| Method                                   | Mixed models analysis       |
| Parameter estimate                       | LSMean Difference           |
| Point estimate                           | 0.6273                      |
| Confidence interval                      |                             |
| level                                    | 95 %                        |
| sides                                    | 2-sided                     |
| lower limit                              | -1.7387                     |
| upper limit                              | 2.9934                      |
| Variability estimate                     | Standard error of the mean  |
| Dispersion value                         | 1.2028                      |

Notes:

[29] - Total participants 167. one participant who did not receive study drug is included in the analysis.

|  |                             |
|--|-----------------------------|
| <b>Statistical analysis title</b>        | Statistical Analysis 6      |
| Statistical analysis description:<br>MCS |                             |
| Comparison groups                        | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis  | 169                         |
| Analysis specification                   | Pre-specified               |
| Analysis type                            | superiority <sup>[30]</sup> |
| P-value                                  | = 0.709                     |
| Method                                   | Mixed models analysis       |
| Parameter estimate                       | LSMean Difference           |
| Point estimate                           | 0.4467                      |
| Confidence interval                      |                             |
| level                                    | 95 %                        |
| sides                                    | 2-sided                     |
| lower limit                              | -1.9097                     |
| upper limit                              | 2.803                       |
| Variability estimate                     | Standard error of the mean  |
| Dispersion value                         | 1.1978                      |

Notes:

[30] - Total participants 169. one participant who did not receive study drug is included in the analysis.

## Secondary: Change from Baseline in ASAS Health Index (ASAS HI)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in ASAS Health Index (ASAS HI) |
|-----------------|---|

End point description:

ASAS HI is a disease-specific health-index instrument designed to assess the impact of interventions for SpA, including axSpA. The 17-item instrument has scores ranging from 0 (good health) to 17 (poor health). Each item consists of one question that the participant needs to respond to with either "I agree" (score of 1) or "I do not agree" (score of 0). A score of "1" is given where the item is affirmed, indicating adverse health. All item scores are summed to give a total score or index.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

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

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-------------------------------------|--------------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 86 <sup>[31]</sup> | 90              | 83              | 81              |
| Units: score on a scale             |                    |                 |                 |                 |
| least squares mean (standard error) | -1.25 (± 0.300)    | -2.30 (± 0.292) | -2.74 (± 0.306) | -2.36 (± 0.311) |

Notes:

[31] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

|   |                             |
|---|-----------------------------|
| Statistical analysis title              | Statistical Analysis 1      |
| Comparison groups                       | Placebo (PBO) v Adalimumab  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[32]</sup> |
| P-value                                 | = 0.012                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -1.05                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.87                       |
| upper limit                             | -0.23                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.416                       |

Notes:

[32] - Total participants 177. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2      |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[33]</sup> |
| P-value                                 | = 0.01                      |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -1.11                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.95                       |
| upper limit                             | -0.27                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.428                       |

Notes:

[33] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Comparison groups                       | IXE80Q2W v Placebo (PBO)    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[34]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -1.49                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -2.32                       |
| upper limit                             | -0.66                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.423                       |

Notes:

[34] - Total participants 170. one participant who did not receive study drug is included in the analysis.

## Secondary: Change from Baseline in the Measure of High Sensitivity C-Reactive Protein (CRP)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in the Measure of High Sensitivity C-Reactive Protein (CRP) |
|-----------------|--|

End point description:

High sensitivity CRP is the measure of acute phase reactant. It will be measured with a high sensitivity assay at the central laboratory to help assess the effect of Ixekizumab on disease activity.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, visit and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

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

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)         | Adalimumab             | IXE80Q2W               | IXE80Q4W               |
|-------------------------------------|-----------------------|------------------------|------------------------|------------------------|
| Subject group type                  | Reporting group       | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed         | 86 <sup>[35]</sup>    | 90                     | 83                     | 81                     |
| Units: Milliragm per Litre (mg/mL)  |                       |                        |                        |                        |
| least squares mean (standard error) | 1.426 ( $\pm$ 1.9244) | -7.202 ( $\pm$ 1.8688) | -6.565 ( $\pm$ 1.9582) | -5.209 ( $\pm$ 1.9803) |

Notes:

[35] - Total participants 87, one participant who did not receive study drug is included in the analysis.

### Statistical analyses

| Statistical analysis title              | Statistical Analysis 1      |
|---|-----------------------------|
| Comparison groups                       | Placebo (PBO) v Adalimumab  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[36]</sup> |
| P-value                                 | = 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -8.628                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -13.885                     |
| upper limit                             | -3.371                      |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 2.6724                      |

Notes:

[36] - Total participants 177. one participant who did not receive study drug is included in the analysis.

| Statistical analysis title              | Statistical Analysis 2      |
|---|-----------------------------|
| Comparison groups                       | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[37]</sup> |
| P-value                                 | = 0.016                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -6.635                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -12.033                     |
| upper limit                             | -1.238                      |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 2.7438                     |

Notes:

[37] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[38]</sup> |
| P-value                                 | = 0.004                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -7.991                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -13.351                     |
| upper limit                             | -2.631                      |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 2.7248                      |

Notes:

[38] - Total participants 169. one participant who did not receive study drug is included in the analysis.

## **Secondary: Change from Baseline in Mobility on the Bath Ankylosing Spondylitis Metrology Index (BASMI)**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Mobility on the Bath Ankylosing Spondylitis Metrology Index (BASMI) |
|-----------------|---|

End point description:

The BASMI is a combined index comprising the following 5 clinical measurements of spinal mobility in participants with rad-axSpA.

- 1) Lateral spinal flexion
- 2)Tragus-to-wall distance
- 3) Lumbar flexion (modified Schrober)
- 4) Maximal intermalleolar distance
- 5)Cervical rotation.

The BASMI includes these 5 measurements that are each scaled to a score of 0 to 10 depending on the result of the assessment (BASMI linear function). The average score of the 5 assessments gives the BASMI linear result. The higher the BASMI score the more severe the participants limitation of movement due to their AS.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

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

End point timeframe:

Baseline, Week 16



| End point values                    | Placebo (PBO)          | Adalimumab             | IXE80Q2W               | IXE80Q4W               |
|-------------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type                  | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed         | 86 <sup>[39]</sup>     | 90                     | 83                     | 81                     |
| Units: score on a scale             |                        |                        |                        |                        |
| least squares mean (standard error) | -0.080 ( $\pm$ 0.0826) | -0.447 ( $\pm$ 0.0800) | -0.408 ( $\pm$ 0.0840) | -0.447 ( $\pm$ 0.0858) |

Notes:

[39] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

| Statistical analysis title              | Statistical Analysis 1      |
|---|-----------------------------|
| Comparison groups                       | Placebo (PBO) v Adalimumab  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[40]</sup> |
| P-value                                 | = 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.367                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.592                      |
| upper limit                             | -0.142                      |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.1143                      |

Notes:

[40] - Total participants 177. one participant who did not receive study drug is included in the analysis.

| Statistical analysis title              | Statistical Analysis 2      |
|---|-----------------------------|
| Comparison groups                       | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[41]</sup> |
| P-value                                 | < 0.001                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.422                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.655                      |
| upper limit                             | -0.189                      |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.1184                      |

Notes:

[41] - Total participants 168. one participant who did not receive study drug is included in the analysis.

| Statistical analysis title | Statistical Analysis 3 |
|----------------------------|------------------------|
|----------------------------|------------------------|

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[42]</sup> |
| P-value                                 | = 0.005                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.329                      |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.558                      |
| upper limit                             | -0.099                      |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.1167                      |

Notes:

[42] - Total participants 170. one participant who did not receive study drug is included in the analysis.

## Secondary: Change from Baseline in Chest Expansion

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Chest Expansion |
|-----------------|---|

End point description:

While participants have their hands resting on or behind the head, the assessor has measured the chest's encircled length by centimeter at the fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in centimeters was recorded. Two tries were recorded. The better measurement (larger difference) of 2 tries (in centimeters) was used for analyses.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

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

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-------------------------------------|--------------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 86 <sup>[43]</sup> | 90              | 83              | 81              |
| Units: Centimeters (cm)             |                    |                 |                 |                 |
| least squares mean (standard error) | 0.06 (± 0.152)     | 0.70 (± 0.148)  | 0.67 (± 0.155)  | 0.49 (± 0.158)  |

Notes:

[43] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

|                            |                            |
|----------------------------|----------------------------|
| Statistical analysis title | Statistical Analysis 1     |
| Comparison groups          | Placebo (PBO) v Adalimumab |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[44]</sup> |
| P-value                                 | = 0.003                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | 0.63                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.22                        |
| upper limit                             | 1.05                        |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.211                       |

Notes:

[44] - Total participants 177. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2      |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[45]</sup> |
| P-value                                 | = 0.051                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | 0.43                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0                           |
| upper limit                             | 0.86                        |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.219                       |

Notes:

[45] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[46]</sup> |
| P-value                                 | = 0.005                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | 0.6                         |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.18                        |
| upper limit                             | 1.03                        |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.215                      |

Notes:

[46] - Total participants 170. one participant who did not receive study drug is included in the analysis.

## Secondary: Change from Baseline in Occiput to Wall Distance

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Occiput to Wall Distance |
|-----------------|--|

End point description:

The participant is to make a maximum effort to touch the head against the wall when standing with heels and back against the wall (occiput). Then the distance from occiput to wall is measured. Two tries will be recorded. The better (smaller) measurement of 2 tries (in centimeters) will be used for analyses.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

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

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-------------------------------------|--------------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 86 <sup>[47]</sup> | 90              | 83              | 81              |
| Units: cm                           |                    |                 |                 |                 |
| least squares mean (standard error) | -0.06 (± 0.232)    | -0.72 (± 0.225) | -0.73 (± 0.236) | -0.69 (± 0.240) |

Notes:

[47] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

|   |                             |
|---|-----------------------------|
| Statistical analysis title              | Statistical Analysis 1      |
| Comparison groups                       | Placebo (PBO) v Adalimumab  |
| Number of subjects included in analysis | 176                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[48]</sup> |
| P-value                                 | = 0.039                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.67                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.3                        |
| upper limit                             | -0.03                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.321                       |

Notes:

[48] - Total participants 177. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2      |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W    |
| Number of subjects included in analysis | 167                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[49]</sup> |
| P-value                                 | = 0.057                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.63                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.28                       |
| upper limit                             | 0.02                        |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.33                        |

Notes:

[49] - Total participants 168. one participant who did not receive study drug is included in the analysis.

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3      |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W    |
| Number of subjects included in analysis | 169                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[50]</sup> |
| P-value                                 | = 0.042                     |
| Method                                  | Mixed models analysis       |
| Parameter estimate                      | LSMean Difference           |
| Point estimate                          | -0.67                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -1.31                       |
| upper limit                             | -0.03                       |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.327                       |

Notes:

[50] - Total participants 170. one participant who did not receive study drug is included in the analysis.

## **Secondary: Change from Baseline in MRI sacroiliac joint(s) (SIJ) Spondyloarthritis Research Consortium of Canada (SPARCC) Score**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in MRI sacroiliac joint(s) (SIJ)<br>Spondyloarthritis Research Consortium of Canada (SPARCC)<br>Score |
|-----------------|--|

End point description:

Both left and right SIJ are scored for bone marrow edema. Each side has 6 slices and each slice has 6 scoring units, and each scoring unit has a score of 0 or 1. Total SIJ SPARCC scores can range from 0 to 72 with higher scores reflecting worse disease.

LSMean was calculated using ANCOVA model with treatment, geographic region, baseline CRP status and baseline value as fixed factors.

APD: All randomized participants with baseline and week 16 SPARCC score.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 16    |           |

| End point values                    | Placebo (PBO)       | Adalimumab           | IXE80Q2W             | IXE80Q4W             |
|-------------------------------------|---------------------|----------------------|----------------------|----------------------|
| Subject group type                  | Reporting group     | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed         | 81                  | 82                   | 77                   | 78                   |
| Units: score on a scale             |                     |                      |                      |                      |
| least squares mean (standard error) | 0.92 ( $\pm$ 0.582) | -4.21 ( $\pm$ 0.568) | -4.25 ( $\pm$ 0.591) | -3.97 ( $\pm$ 0.590) |

### Statistical analyses

| Statistical analysis title              | Statistical Analysis 1     |
|---|----------------------------|
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 163                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -5.13                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -6.7                       |
| upper limit                             | -3.5                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.806                      |

| Statistical analysis title              | Statistical Analysis 2   |
|---|--------------------------|
| Comparison groups                       | Placebo (PBO) v IXE80Q4W |
| Number of subjects included in analysis | 159                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.001                  |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | LSMean Difference        |
| Point estimate                          | -4.89                    |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -6.5                       |
| upper limit          | -3.3                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.812                      |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3     |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W   |
| Number of subjects included in analysis | 158                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -5.17                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -6.8                       |
| upper limit                             | -3.6                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.816                      |

### **Secondary: Change from Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) |
|-----------------|--|

#### End point description:

The MASES is an index used to measure the severity of enthesitis. The MASES assesses 13 sites for enthesitis using a score of "0" for no activity or "1" for activity. Sites assessed include costochondral 1 (right/left), costochondral 7 (right/left), spinal iliaca anterior superior (right/left), crista iliaca (right/left), spina iliaca posterior (right/left), processus spinosus L5, and Achilles tendon proximal insertion (right/left). The MASES is the sum of all site scores (range 0 to 13); higher scores indicate more severe enthesitis.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants with baseline MASES score > 0.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 16    |           |

| <b>End point values</b>             | Placebo (PBO)      | Adalimumab         | IXE80Q2W           | IXE80Q4W           |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type                  | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed         | 56                 | 51                 | 50                 | 49                 |
| Units: score on a scale             |                    |                    |                    |                    |
| least squares mean (standard error) | -2.1 ( $\pm$ 0.34) | -2.6 ( $\pm$ 0.34) | -2.4 ( $\pm$ 0.35) | -2.3 ( $\pm$ 0.36) |

## Statistical analyses

| <b>Statistical analysis title</b>       | Statistical Analysis 1     |
|---|----------------------------|
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 107                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.317                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.5                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.4                       |
| upper limit                             | 0.5                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.48                       |

| <b>Statistical analysis title</b>       | Statistical Analysis 2     |
|---|----------------------------|
| Comparison groups                       | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis | 105                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.683                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.2                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.1                       |
| upper limit                             | 0.8                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.48                       |

| <b>Statistical analysis title</b> | Statistical Analysis 3   |
|-----------------------------------|--------------------------|
| Comparison groups                 | Placebo (PBO) v IXE80Q2W |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 106                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.5                      |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.3                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.3                       |
| upper limit                             | 0.6                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.48                       |

## Secondary: Change from Baseline in SPARCC Enthesitis Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in SPARCC Enthesitis Score |
|-----------------|---|

End point description:

The SPARCC enthesitis is an index used to measure the severity of enthesitis. The SPARCC assesses 16 sites for enthesitis using a score of "0" for no activity or "1" for activity. Sites assessed include Medial epicondyle (left/right [L/R]), Lateral epicondyle (L/R), Supraspinatus insertion into greater tuberosity of humerus (L/R), Greater trochanter (L/R), Quadriceps insertion into superior border of patella (L/R), Patellar ligament insertion into inferior pole of patella or tibial tubercle (L/R), Achilles tendon insertion into calcaneum (L/R), and Plantar fascia insertion into calcaneum (L/R). The SPARCC is the sum of all site scores (range 0 to 16). Higher scores indicate more severe enthesitis.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants with baseline SPARCC score > 0.

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

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)   | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 41              | 40              | 35              | 40              |
| Units: score on a scale             |                 |                 |                 |                 |
| least squares mean (standard error) | -2.1 (± 0.40)   | -2.9 (± 0.40)   | -2.6 (± 0.43)   | -2.7 (± 0.40)   |

## Statistical analyses

|                            |                            |
|----------------------------|----------------------------|
| Statistical analysis title | Statistical Analysis 1     |
| Comparison groups          | Placebo (PBO) v Adalimumab |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 81                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.154                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.8                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.9                       |
| upper limit                             | 0.3                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.56                       |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2     |
| Comparison groups                       | IXE80Q4W v Placebo (PBO)   |
| Number of subjects included in analysis | 81                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.255                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.6                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.8                       |
| upper limit                             | 0.5                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.56                       |

|   |                          |
|---|--------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3   |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W |
| Number of subjects included in analysis | 76                       |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.398                  |
| Method                                  | Mixed models analysis    |
| Parameter estimate                      | LSMean Difference        |
| Point estimate                          | -0.5                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -1.6                     |
| upper limit                             | 0.7                      |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.58                       |

## Secondary: Change from Baseline in Severity of Peripheral Arthritis by Tender (TJC)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Severity of Peripheral Arthritis by Tender (TJC) |
|-----------------|--|

End point description:

The number of tender and painful joints was determined by examination of 46 joints (23 joints on each side of the participants body. The 46 joints are assessed and classified as tender or not tender. sum of all joints checked to be tender/painful divided by number of evaluable joints which is multiplied by 46 to obtain TJC score. The scores ranges from 0 (no tender/painful joints) to 46 (all joints tender/painful).

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants with baseline TJC > 0.

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

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)   | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 49              | 45              | 44              |
| Units: score on a scale             |                 |                 |                 |                 |
| least squares mean (standard error) | -2.0 (± 0.53)   | -2.2 (± 0.55)   | -3.3 (± 0.58)   | -2.5 (± 0.58)   |

## Statistical analyses

|   |                            |
|---|----------------------------|
| Statistical analysis title              | Statistical Analysis 1     |
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 100                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.783                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.2                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.7                       |
| upper limit                             | 1.3                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.76                       |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2     |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis | 95                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.55                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.5                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2                         |
| upper limit                             | 1.1                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.78                       |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3     |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W   |
| Number of subjects included in analysis | 96                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.091                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -1.3                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.8                       |
| upper limit                             | 0.2                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.77                       |

## Secondary: Number of Participants with Anterior Uveitis or Uveitis Flares

|  |  |
|--|--|
| End point title  | Number of Participants with Anterior Uveitis or Uveitis Flares |
| End point description:   |  |
| Anterior uveitis is an inflammation of the middle layer of the eye which includes the iris (colored part of the eye) and the adjacent tissue, known as the ciliary body. |  |
| APD: All Randomized Participants.  |  |
| End point type   | Secondary  |

End point timeframe:  
Baseline through Week 16

| End point values             | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|------------------------------|--------------------|-----------------|-----------------|-----------------|
| Subject group type           | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed  | 86 <sup>[51]</sup> | 90              | 83              | 81              |
| Units: Count of Participants |                    |                 |                 |                 |
| number (not applicable)      | 0                  | 0               | 0               | 1               |

Notes:

[51] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Fatigue Numeric Rating Scale (NRS) Score

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in the Fatigue Numeric Rating Scale (NRS) Score |
|-----------------|--|

End point description:

The Fatigue Severity NRS is a participant-administered, single-item, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no fatigue" and 10 representing "as bad as you can imagine". Participants rate their fatigue (feeling tired or worn out) by circling the one number that describes their worst level of fatigue during the previous 24 hours.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

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

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-------------------------------------|--------------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 86 <sup>[52]</sup> | 90              | 83              | 81              |
| Units: score on a scale             |                    |                 |                 |                 |
| least squares mean (standard error) | -1.4 (± 0.23)      | -2.2 (± 0.23)   | -2.1 (± 0.24)   | -2.5 (± 0.24)   |

Notes:

[52] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

|                            |                            |
|----------------------------|----------------------------|
| Statistical analysis title | Statistical Analysis 1     |
| Comparison groups          | Placebo (PBO) v Adalimumab |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 176                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.027                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.7                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.3                       |
| upper limit                             | -0.1                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.32                       |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2     |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis | 167                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.002                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -1                         |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -1.7                       |
| upper limit                             | -0.4                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.33                       |

|   |                          |
|---|--------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3   |
| Comparison groups                       | IXE80Q2W v Placebo (PBO) |
| Number of subjects included in analysis | 169                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.035                  |
| Method                                  | Mixed models analysis    |
| Parameter estimate                      | LSMean Difference        |
| Point estimate                          | -0.7                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -1.3                     |
| upper limit                             | 0                        |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.33                       |

## Secondary: Change from Baseline in the Jenkins Sleep Evaluation Questionnaire (JSEQ)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the Jenkins Sleep Evaluation Questionnaire (JSEQ) |
|-----------------|---|

### End point description:

The JSEQ is a 4-item scale designed to estimate sleep problems in clinical research. The JSEQ assesses the frequency of sleep disturbance in 4 categories: 1) trouble falling asleep, 2) waking up several times during the night, 3) having trouble staying asleep (including waking up far too early), and 4) waking up after the usual amount of sleep feeling tired and worn out. Participants report the number of days they experience each of these problems in the past month on a 6-point Likert scale ranging from 0 = "no days" to 5 = "22-30 days." The total JSEQ score ranges from 0 to 20, with higher scores indicating greater sleep disturbance.

LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.

APD: All Randomized Participants.

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

### End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)      | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-------------------------------------|--------------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group    | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 86 <sup>[53]</sup> | 90              | 83              | 81              |
| Units: score on a scale             |                    |                 |                 |                 |
| least squares mean (standard error) | -1.5 (± 0.41)      | -2.7 (± 0.40)   | -3.0 (± 0.42)   | -2.5 (± 0.43)   |

### Notes:

[53] - Total participants 87, one participant who did not receive study drug is included in the analysis.

## Statistical analyses

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1     |
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 176                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.041                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -1.2                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.3                       |
| upper limit                             | 0                          |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.57                       |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2     |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis | 167                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.125                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -0.9                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.1                       |
| upper limit                             | 0.3                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.59                       |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3     |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W   |
| Number of subjects included in analysis | 169                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.013                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -1.4                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.6                       |
| upper limit                             | -0.3                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.58                       |

## Secondary: Change from Baseline in the Work Productivity Activity Impairment Spondyloarthritis (WPAI-SpA) Scores

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in the Work Productivity Activity Impairment Spondyloarthritis (WPAI-SpA) Scores |
|-----------------|---|

### End point description:

The WPAI-SpA consists of 6 questions to determine employment status, hours missed from work because of SpA, hours missed from work for other reasons, hours actually worked, the degree to which SpA affected work productivity while at work, and the degree to which SpA affected activities outside of work. The WPAI-SpA has been validated in the rad-axSpA patient population. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in



activities performed outside of work. The computed percentage range for each sub-scale was from 0-100. Greater scores indicate greater impairment and less productivity.

LSMean was calculated using ANCOVA model with treatment, geographic region, baseline CRP status and baseline value as fixed factors.

APD: All Randomized Participants with baseline and week 16 WPAI score.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 16    |           |

| End point values                    | Placebo (PBO)    | Adalimumab       | IXE80Q2W         | IXE80Q4W         |
|-------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type                  | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed         | 86               | 88               | 83               | 80               |
| Units: score on a scale             |                  |                  |                  |                  |
| least squares mean (standard error) |                  |                  |                  |                  |
| Overall Work Impairment Score       | -17.82 (± 3.254) | -21.44 (± 2.921) | -24.06 (± 3.299) | -21.36 (± 3.061) |
| Percentage of Activity Impairment   | -14.1 (± 2.28)   | -21.1 (± 2.22)   | -23.4 (± 2.30)   | -23.0 (± 2.35)   |

## Statistical analyses

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1     |
| Statistical analysis description:       |                            |
| Overall Work Impairment Score           |                            |
| Subjects in analysis: 110               |                            |
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 174                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.408                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -3.62                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -12.21                     |
| upper limit                             | 4.98                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 4.36                       |

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2   |
| Statistical analysis description: |                          |
| Overall Work Impairment Score.    |                          |
| Subjects in Analysis: 105         |                          |
| Comparison groups                 | Placebo (PBO) v IXE80Q4W |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 166                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.422                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -3.53                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -12.2                      |
| upper limit                             | 5.13                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 4.393                      |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>   | Statistical Analysis 3     |
| Statistical analysis description:<br>Overall Work Impairment Score<br>Subjects in this Analysis: 97 |                            |
| Comparison groups   | Placebo (PBO) v IXE80Q2W   |
| Number of subjects included in analysis   | 169                        |
| Analysis specification  | Pre-specified              |
| Analysis type   | superiority                |
| P-value   | = 0.175                    |
| Method  | ANCOVA                     |
| Parameter estimate  | LSMean Difference          |
| Point estimate  | -6.24                      |
| Confidence interval   |                            |
| level   | 95 %                       |
| sides   | 2-sided                    |
| lower limit   | -15.27                     |
| upper limit   | 2.8                        |
| Variability estimate  | Standard error of the mean |
| Dispersion value  | 4.582                      |

|  |                            |
|--|----------------------------|
| <b>Statistical analysis title</b>                                      | Statistical Analysis 4     |
| Statistical analysis description:<br>Percentage of Activity Impairment |                            |
| Comparison groups  | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis                                | 174                        |
| Analysis specification   | Pre-specified              |
| Analysis type  | superiority                |
| P-value  | < 0.001                    |
| Method   | ANCOVA                     |
| Parameter estimate   | LSMean Difference          |
| Point estimate   | -7                         |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -13.2                      |
| upper limit          | -0.7                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 3.16                       |

|  |                            |
|--|----------------------------|
| <b>Statistical analysis title</b>                                      | Statistical Analysis 5     |
| Statistical analysis description:<br>Percentage of Activity Impairment |                            |
| Comparison groups  | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis                                | 166                        |
| Analysis specification   | Pre-specified              |
| Analysis type  | superiority                |
| P-value  | < 0.001                    |
| Method   | ANCOVA                     |
| Parameter estimate   | LSMean Difference          |
| Point estimate   | -8.9                       |
| Confidence interval  |                            |
| level  | 95 %                       |
| sides  | 2-sided                    |
| lower limit  | -15.2                      |
| upper limit  | -2.5                       |
| Variability estimate   | Standard error of the mean |
| Dispersion value   | 3.22                       |

|  |                            |
|--|----------------------------|
| <b>Statistical analysis title</b>                                      | Statistical Analysis 6     |
| Statistical analysis description:<br>Percentage of Activity Impairment |                            |
| Comparison groups  | Placebo (PBO) v IXE80Q2W   |
| Number of subjects included in analysis                                | 169                        |
| Analysis specification   | Pre-specified              |
| Analysis type  | superiority                |
| P-value  | < 0.001                    |
| Method   | ANCOVA                     |
| Parameter estimate   | LSMean Difference          |
| Point estimate   | -9.3                       |
| Confidence interval  |                            |
| level  | 95 %                       |
| sides  | 2-sided                    |
| lower limit  | -15.5                      |
| upper limit  | -3                         |
| Variability estimate   | Standard error of the mean |
| Dispersion value   | 3.19                       |

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**Secondary: Change from Baseline in ASAS-Nonsteroidal Anti-Inflammatory Drug (NSAID) Score**

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|                 |  |
|-----------------|--|
| End point title | Change from Baseline in ASAS-Nonsteroidal Anti-Inflammatory Drug (NSAID) Score |
|-----------------|--|

End point description:

ASAS-NSAID score is used to present the NSAID intake by considering the type of NSAID, the total dose, & the number of days taking NSAID during a period of interest (PI).. ASAS-NSAID score=(equivalent NSAID score)x(days of intake during PI)x(days per week)/(PI in days). Higher scores indicate greater NSAIDs intake. 0= no intake, 100 = equivalent NSAID intake.

Participants in Extended Treatment Period Population Who had NSAID Intake at Baseline.

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

End point timeframe:

Baseline, Week 52

---

| End point values                     | PBO/IXE              | Adalimumab/IXE       | IXE80Q4W/IXE80Q4W    | IXE80Q2W/IXE80Q2W    |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 78                   | 80                   | 71                   | 76                   |
| Units: score on a scale              |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | -10.28 (± 27.472)    | -5.91 (± 20.861)     | -7.62 (± 25.430)     | -9.91 (± 27.940)     |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of Participants with Anti Ixekizumab Antibodies**

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|                 |  |
|-----------------|--|
| End point title | Number of Participants with Anti Ixekizumab Antibodies |
|-----------------|--|

End point description:

A treatment emergent - antidrug antibody (TE-ADA) positive patient is defined as: a) a patient with a  $\geq 4$ -fold increase over a positive baseline antibody titer; or b) for a negative baseline titer, a patient with an increase from the baseline to a level of  $\geq 1:10$ .

APD: All randomized participants.

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

End point timeframe:

Week 16

---

| End point values            | Placebo (PBO)   | Adalimumab      | IXE80Q2W        | IXE80Q4W        |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 86              | 90              | 83              | 81              |
| Units: participants         |                 |                 |                 |                 |
| number (not applicable)     | 2               | 5               | 2               | 2               |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics: Trough Ixekizumab Concentration at Steady State (Ctough ss)

|  |   |
|--|---|
| End point title  | Pharmacokinetics: Trough Ixekizumab Concentration at Steady State (Ctough ss) |
| End point description:<br>APD: All randomized participants who received at least one dose of Ixekizumab. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Week 16  |   |

| End point values                                    | IXE160/80Q4W         | IXE160/80Q2W         |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                                  | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                         | 39                   | 38                   |  |  |
| Units: microgram per millilitre (µg/mL)             |                      |                      |  |  |
| geometric mean (geometric coefficient of variation) | 3.88 (± 55)          | 11.3 (± 43)          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Severity of Peripheral Arthritis by Swollen Joint Count (SJC)

|   |   |
|---|---|
| End point title   | Change from Baseline in Severity of Peripheral Arthritis by Swollen Joint Count (SJC) |
| End point description:<br>The number of swollen joints was determined by examination of 44 joints (22 joints on each side of the participants body. The 44 joints are assessed and classified as swollen or not swollen. "sum of all joints checked to be swollen" divided by "number of evaluable joints" and then multiplied by 44 to obtain SJC score. The SJC score ranges from 0 (no swollen joints) to 44 (all joints swollen).<br><br>LSMean was calculated using MMRM model with treatment, geographic region, baseline CRP status, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.<br><br>APD: All Randomized Participants with baseline SJC > 0. |   |
| End point type  | Secondary   |

End point timeframe:

Baseline, Week 16

| End point values                    | Placebo (PBO)      | Adalimumab         | IXE80Q2W           | IXE80Q4W           |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type                  | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed         | 22                 | 23                 | 20                 | 24                 |
| Units: score on a scale             |                    |                    |                    |                    |
| least squares mean (standard error) | -1.7 ( $\pm$ 0.55) | -2.7 ( $\pm$ 0.53) | -2.7 ( $\pm$ 0.57) | -3.6 ( $\pm$ 0.53) |

## Statistical analyses

| Statistical analysis title              | Statistical Analysis 1     |
|---|----------------------------|
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 45                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.166                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -1.1                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.6                       |
| upper limit                             | 0.4                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.76                       |

| Statistical analysis title              | Statistical Analysis 2     |
|---|----------------------------|
| Comparison groups                       | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis | 46                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.11                     |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -1.9                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -3.4                       |
| upper limit                             | -0.4                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.73                       |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3     |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W   |
| Number of subjects included in analysis | 42                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | = 0.182                    |
| Method                                  | Mixed models analysis      |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -1                         |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.6                       |
| upper limit                             | 0.5                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.77                       |

### Secondary: Change from Baseline in Magnetic Resonance Imaging (MRI) of the Spine (Spondyloarthritis Research Consortium of Canada [SPARCC] score)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Magnetic Resonance Imaging (MRI) of the Spine (Spondyloarthritis Research Consortium of Canada [SPARCC] score) |
|-----------------|--|

#### End point description:

MRI score of spine was assessed using SPARCC method. All 23 disco-vertebral units (DVUs) of the spine (from C2 to S1) are scored for bone marrow edema. A single DVU has a scoring range of 0 to 18, bringing the maximum total score to 414, with higher scores reflecting worse disease. Scoring was performed by central readers.

LSMean was calculated using ANCOVA model with treatment, geographic region, baseline CRP status and baseline value as fixed factors.

APD: All Randomized participants with baseline and week 16 SPARCC MRI score for spine.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 16    |           |

| End point values                    | Placebo (PBO)   | Adalimumab       | IXE80Q2W        | IXE80Q4W         |
|-------------------------------------|-----------------|------------------|-----------------|------------------|
| Subject group type                  | Reporting group | Reporting group  | Reporting group | Reporting group  |
| Number of subjects analysed         | 81              | 82               | 76              | 78               |
| Units: score on a scale             |                 |                  |                 |                  |
| least squares mean (standard error) | -1.51 (± 1.147) | -11.57 (± 1.113) | -9.58 (± 1.168) | -11.02 (± 1.160) |

## Statistical analyses

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1     |
| Comparison groups                       | Placebo (PBO) v Adalimumab |
| Number of subjects included in analysis | 163                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -10.07                     |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -13.2                      |
| upper limit                             | -6.9                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 1.588                      |

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2     |
| Comparison groups                       | Placebo (PBO) v IXE80Q4W   |
| Number of subjects included in analysis | 159                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority                |
| P-value                                 | < 0.001                    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LSMean Difference          |
| Point estimate                          | -9.51                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -12.6                      |
| upper limit                             | -6.4                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 1.591                      |

|   |                          |
|---|--------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 3   |
| Comparison groups                       | Placebo (PBO) v IXE80Q2W |
| Number of subjects included in analysis | 157                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.001                  |
| Method                                  | ANCOVA                   |
| Parameter estimate                      | LSMean Difference        |
| Point estimate                          | -8.08                    |



|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -11.2                      |
| upper limit          | -4.9                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 1.603                      |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 76 Weeks

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug. There are gender specific adverse events, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 21.1   |

### Reporting groups

|                                |   |
|--------------------------------|---|
| Reporting group title          | IXE80Q4W-blinded treatment period           |
| Reporting group description: - |   |
| Reporting group title          | IXE80Q2W-blinded treatment period           |
| Reporting group description: - |   |
| Reporting group title          | PBO-blinded treatment period                |
| Reporting group description: - |   |
| Reporting group title          | IXE80Q2W/IXE80Q2W-extended treatment period |
| Reporting group description: - |   |
| Reporting group title          | ADA-blinded treatment period                |
| Reporting group description: - |   |
| Reporting group title          | IXE80Q4W/IXE80Q4W-extended treatment period |
| Reporting group description: - |   |
| Reporting group title          | PBO/IXE-extended treatment period           |
| Reporting group description: - |   |
| Reporting group title          | ADA/PBO-washout treatment period            |
| Reporting group description: - |   |
| Reporting group title          | ADA/PBO/IXE-extended treatment period       |
| Reporting group description: - |   |
| Reporting group title          | IXE80Q2W-follow-up period                   |
| Reporting group description: - |   |
| Reporting group title          | IXE80Q4W-follow-up period                   |
| Reporting group description: - |   |
| Reporting group title          | PBO-follow-up period                        |
| Reporting group description: - |   |

| Serious adverse events  | IXE80Q4W-blinded treatment period | IXE80Q2W-blinded treatment period | PBO-blinded treatment period |
|---|-----------------------------------|-----------------------------------|------------------------------|
| Total subjects affected by serious adverse events                   |                                   |                                   |                              |
| subjects affected / exposed   | 1 / 81 (1.23%)                    | 1 / 83 (1.20%)                    | 0 / 86 (0.00%)               |
| number of deaths (all causes)                                       | 0                                 | 0                                 | 0                            |
| number of deaths resulting from adverse events                      | 0                                 | 0                                 | 0                            |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |                                   |                              |

|  |                |                |                |
|--|----------------|----------------|----------------|
| bladder cancer                                     |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| parathyroid tumour benign                          |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| skin papilloma                                     |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                     |                |                |                |
| blood creatine phosphokinase<br>increased          |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural<br>complications  |                |                |                |
| ankle fracture                                     |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| avulsion fracture                                  |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| cervical vertebral fracture                        |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| post procedural haematoma                          |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| radius fracture                                    |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| road traffic accident                              |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                                  |                |                |                |
| atrioventricular block complete                    |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                           |                |                |                |
| cerebral haemorrhage                               |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| subarachnoid haemorrhage                           |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (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          |
| Blood and lymphatic system disorders            |                |                |                |
| lymphadenitis                                   |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (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          |
| Reproductive system and breast disorders        |                |                |                |
| adnexal torsion                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed <sup>[1]</sup>      | 0 / 13 (0.00%) | 0 / 19 (0.00%) | 0 / 15 (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          |
| Gastrointestinal disorders                      |                |                |                |
| crohn's disease                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 83 (1.20%) | 0 / 86 (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          |
| dyspepsia                                       |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 83 (1.20%) | 0 / 86 (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          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| erythema multiforme                             |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 83 (1.20%) | 0 / 86 (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          |
| Renal and urinary disorders                     |                |                |                |
| nephrolithiasis                                 |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders    |                |                |                |
| arthritis  |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| osteoarthritis                                     |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| plica syndrome                                     |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                        |                |                |                |
| appendicitis                                       |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| cellulitis   |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| gastroenteritis                                    |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 83 (1.20%) | 0 / 86 (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          |
| pneumonia haemophilus                           |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (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          |
| tonsillitis                                     |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 0 / 83 (0.00%) | 0 / 86 (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          |
| urinary tract infection                         |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 83 (0.00%) | 0 / 86 (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          |

| <b>Serious adverse events</b>                                       | IXE80Q2W/IXE80Q2W-extended treatment period | ADA-blinded treatment period | IXE80Q4W/IXE80Q4W-extended treatment period |
|---|---|------------------------------|---|
| Total subjects affected by serious adverse events                   |   |                              |   |
| subjects affected / exposed   | 3 / 79 (3.80%)                              | 3 / 90 (3.33%)               | 4 / 78 (5.13%)                              |
| number of deaths (all causes)                                       | 0   | 0                            | 0   |
| number of deaths resulting from adverse events                      | 0   | 0                            | 0   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                              |   |
| bladder cancer  |   |                              |   |
| alternative dictionary used: MedDRA 21.1                            |   |                              |   |
| subjects affected / exposed   | 0 / 79 (0.00%)                              | 0 / 90 (0.00%)               | 0 / 78 (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                                       |
| parathyroid tumour benign   |   |                              |   |
| alternative dictionary used: MedDRA 21.1                            |   |                              |   |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| skin papilloma                                  |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 1 / 79 (1.27%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| Investigations                                  |                |                |                |
| blood creatine phosphokinase increased          |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| ankle fracture                                  |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 1 / 90 (1.11%) | 0 / 78 (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          |
| avulsion fracture                               |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 1 / 79 (1.27%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| cervical vertebral fracture                     |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| post procedural haematoma                       |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |



|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed  | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| radius fracture<br>alternative dictionary used:<br>MedDRA 21.1                                       |                |                |                |
| subjects affected / exposed  | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all  | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all   | 0 / 0          | 0 / 0          | 0 / 0          |
| road traffic accident<br>alternative dictionary used:<br>MedDRA 21.1                                 |                |                |                |
| subjects affected / exposed  | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all  | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all   | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders<br>atrioventricular block complete<br>alternative dictionary used:<br>MedDRA 21.1  |                |                |                |
| subjects affected / exposed  | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| Nervous system disorders<br>cerebral haemorrhage<br>alternative dictionary used:<br>MedDRA 21.1      |                |                |                |
| subjects affected / exposed  | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| subarachnoid haemorrhage<br>alternative dictionary used:<br>MedDRA 21.1                              |                |                |                |
| subjects affected / exposed  | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| Blood and lymphatic system disorders<br>lymphadenitis<br>alternative dictionary used:<br>MedDRA 21.1 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| Reproductive system and breast disorders        |                |                |                |
| adnexal torsion                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed <sup>[1]</sup>      | 0 / 18 (0.00%) | 1 / 17 (5.88%) | 0 / 13 (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          |
| Gastrointestinal disorders                      |                |                |                |
| crohn's disease                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| dyspepsia                                       |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| erythema multiforme                             |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| Renal and urinary disorders                     |                |                |                |
| nephrolithiasis                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| arthritis  |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| osteoarthritis                                     |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| plica syndrome                                     |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 1 / 79 (1.27%) | 0 / 90 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                        |                |                |                |
| appendicitis                                       |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 79 (0.00%) | 1 / 90 (1.11%) | 0 / 78 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| cellulitis   |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| gastroenteritis                                    |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |
| subjects affected / exposed                        | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| pneumonia haemophilus                              |                |                |                |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| tonsillitis                                     |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 1 / 79 (1.27%) | 0 / 90 (0.00%) | 0 / 78 (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          |
| urinary tract infection                         |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 90 (0.00%) | 0 / 78 (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          |

| <b>Serious adverse events</b>                                       | PBO/IXE-extended treatment period | ADA/PBO-washout treatment period | ADA/PBO/IXE-extended treatment period |
|---|-----------------------------------|----------------------------------|---------------------------------------|
| Total subjects affected by serious adverse events                   |                                   |                                  |                                       |
| subjects affected / exposed   | 4 / 86 (4.65%)                    | 0 / 88 (0.00%)                   | 7 / 86 (8.14%)                        |
| number of deaths (all causes)                                       | 0                                 | 0                                | 0                                     |
| number of deaths resulting from adverse events                      | 0                                 | 0                                | 0                                     |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |                                  |                                       |
| bladder cancer  |                                   |                                  |                                       |
| alternative dictionary used: MedDRA 21.1                            |                                   |                                  |                                       |
| subjects affected / exposed   | 0 / 86 (0.00%)                    | 0 / 88 (0.00%)                   | 1 / 86 (1.16%)                        |
| occurrences causally related to treatment / all                     | 0 / 0                             | 0 / 0                            | 0 / 1                                 |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0                            | 0 / 0                                 |
| parathyroid tumour benign   |                                   |                                  |                                       |
| alternative dictionary used: MedDRA 21.1                            |                                   |                                  |                                       |
| subjects affected / exposed   | 0 / 86 (0.00%)                    | 0 / 88 (0.00%)                   | 1 / 86 (1.16%)                        |
| occurrences causally related to treatment / all                     | 0 / 0                             | 0 / 0                            | 0 / 1                                 |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0                            | 0 / 0                                 |
| skin papilloma  |                                   |                                  |                                       |
| alternative dictionary used: MedDRA 21.1                            |                                   |                                  |                                       |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| Investigations                                  |                |                |                |
| blood creatine phosphokinase increased          |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| Injury, poisoning and procedural complications  |                |                |                |
| ankle fracture                                  |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| avulsion fracture                               |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| cervical vertebral fracture                     |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 1 / 86 (1.16%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| post procedural haematoma                       |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| radius fracture                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| road traffic accident                           |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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                               |                |                |                |
| atrioventricular block complete                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 1 / 86 (1.16%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| Nervous system disorders                        |                |                |                |
| cerebral haemorrhage                            |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| subarachnoid haemorrhage                        |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| lymphadenitis                                   |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 1 / 86 (1.16%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| Reproductive system and breast disorders        |                |                |                |
| adnexal torsion                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed <sup>[1]</sup>      | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 16 (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          |
| Gastrointestinal disorders                      |                |                |                |
| crohn's disease                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| dyspepsia                                       |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| erythema multiforme                             |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| Renal and urinary disorders                     |                |                |                |
| nephrolithiasis                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| arthritis                                       |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| osteoarthritis                                  |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 86 (1.16%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| plica syndrome                                  |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| Infections and infestations                     |                |                |                |
| appendicitis                                    |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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                                      |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 1 / 86 (1.16%) | 0 / 88 (0.00%) | 0 / 86 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| gastroenteritis                                 |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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 haemophilus                           |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 1 / 86 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| tonsillitis                                     |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |
| urinary tract infection                         |                |                |                |
| alternative dictionary used: MedDRA 21.1        |                |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%) | 0 / 88 (0.00%) | 0 / 86 (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          |

| <b>Serious adverse events</b>                                       | IXE80Q2W-follow-up period | IXE80Q4W-follow-up period | PBO-follow-up period |
|---|---------------------------|---------------------------|----------------------|
| Total subjects affected by serious adverse events                   |                           |                           |                      |
| subjects affected / exposed   | 0 / 24 (0.00%)            | 0 / 16 (0.00%)            | 0 / 1 (0.00%)        |
| number of deaths (all causes)                                       | 0                         | 0                         | 0                    |
| number of deaths resulting from adverse events                      | 0                         | 0                         | 0                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                           |                      |
| bladder cancer  |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed   | 0 / 24 (0.00%)            | 0 / 16 (0.00%)            | 0 / 1 (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                |
| parathyroid tumour benign   |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed   | 0 / 24 (0.00%)            | 0 / 16 (0.00%)            | 0 / 1 (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                |
| skin papilloma  |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed   | 0 / 24 (0.00%)            | 0 / 16 (0.00%)            | 0 / 1 (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                |
| Investigations  |                           |                           |                      |
| blood creatine phosphokinase increased                              |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| Injury, poisoning and procedural complications  |                |                |               |
| ankle fracture                                  |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| avulsion fracture                               |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| cervical vertebral fracture                     |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| post procedural haematoma                       |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| radius fracture                                 |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| road traffic accident                           |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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                               |                |                |               |
| atrioventricular block complete                 |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| Nervous system disorders                        |                |                |               |
| cerebral haemorrhage                            |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| subarachnoid haemorrhage                        |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| Blood and lymphatic system disorders            |                |                |               |
| lymphadenitis                                   |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |
| Reproductive system and breast disorders        |                |                |               |
| adnexal torsion                                 |                |                |               |
| alternative dictionary used: MedDRA 21.1        |                |                |               |
| subjects affected / exposed <sup>[1]</sup>      | 0 / 9 (0.00%)  | 0 / 3 (0.00%)  | 0 / 1 (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         |
| Gastrointestinal disorders                      |                |                |               |
| crohn's disease                                 |                |                |               |

|  |                |                |               |
|--|----------------|----------------|---------------|
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| dyspepsia  |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Skin and subcutaneous tissue disorders             |                |                |               |
| erythema multiforme                                |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Renal and urinary disorders                        |                |                |               |
| nephrolithiasis                                    |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue disorders    |                |                |               |
| arthritis  |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| osteoarthritis                                     |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| plica syndrome                                     |                |                |               |

|  |                |                |               |
|--|----------------|----------------|---------------|
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Infections and infestations                        |                |                |               |
| appendicitis                                       |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| cellulitis   |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| gastroenteritis                                    |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| pneumonia haemophilus                              |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| tonsillitis  |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |
| subjects affected / exposed                        | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| urinary tract infection                            |                |                |               |
| alternative dictionary used:<br>MedDRA 21.1        |                |                |               |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 24 (0.00%) | 0 / 16 (0.00%) | 0 / 1 (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         |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Gender specific adverse event, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

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

| <b>Non-serious adverse events</b>  | IXE80Q4W-blinded treatment period              | IXE80Q2W-blinded treatment period              | PBO-blinded treatment period                   |
|--|--|--|--|
| Total subjects affected by non-serious adverse events  |  |  |  |
| subjects affected / exposed  | 11 / 81 (13.58%)                               | 18 / 83 (21.69%)                               | 12 / 86 (13.95%)                               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>uterine leiomyoma<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[2]</sup><br>occurrences (all)   | 0 / 13 (0.00%)<br>0                            | 0 / 19 (0.00%)<br>0                            | 0 / 15 (0.00%)<br>0                            |
| General disorders and administration site conditions<br>injection site reaction<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)   | 0 / 81 (0.00%)<br>0                            | 7 / 83 (8.43%)<br>37                           | 2 / 86 (2.33%)<br>33                           |
| Eye disorders<br>ocular discomfort<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)  | 0 / 81 (0.00%)<br>0                            | 0 / 83 (0.00%)<br>0                            | 0 / 86 (0.00%)<br>0                            |
| Reproductive system and breast disorders<br>adnexal torsion<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[3]</sup><br>occurrences (all)<br><br>menopausal symptoms<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[4]</sup><br>occurrences (all) | 0 / 13 (0.00%)<br>0<br><br>0 / 13 (0.00%)<br>0 | 0 / 19 (0.00%)<br>0<br><br>0 / 19 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0 |

|  |   |   |   |
|--|---|---|---|
| menstruation irregular<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[5]</sup><br>occurrences (all)   | 0 / 13 (0.00%)<br>0   | 0 / 19 (0.00%)<br>0   | 1 / 15 (6.67%)<br>1   |
| Gastrointestinal disorders<br>diarrhoea<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)   | 0 / 81 (0.00%)<br>0   | 2 / 83 (2.41%)<br>2   | 2 / 86 (2.33%)<br>2   |
| Musculoskeletal and connective tissue disorders<br>back pain<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)  | 0 / 81 (0.00%)<br>0   | 1 / 83 (1.20%)<br>1   | 1 / 86 (1.16%)<br>1   |
| Infections and infestations<br>nasopharyngitis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)<br><br>upper respiratory tract infection<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)<br><br>vaginal infection<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[6]</sup><br>occurrences (all) | 6 / 81 (7.41%)<br>6<br><br>7 / 81 (8.64%)<br>8<br><br>0 / 13 (0.00%)<br>0 | 5 / 83 (6.02%)<br>6<br><br>4 / 83 (4.82%)<br>4<br><br>0 / 19 (0.00%)<br>0 | 6 / 86 (6.98%)<br>6<br><br>4 / 86 (4.65%)<br>5<br><br>0 / 15 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>   | IXE80Q2W/IXE80Q2<br>W-extended<br>treatment period | ADA-blinded<br>treatment period | IXE80Q4W/IXE80Q4<br>W-extended<br>treatment period |
|---|--|---------------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 21 / 79 (26.58%)                                   | 16 / 90 (17.78%)                | 14 / 78 (17.95%)                                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>uterine leiomyoma<br>alternative dictionary used:<br>MedDRA 21.1 |  |                                 |  |

|  |   |   |   |
|--|---|---|---|
| subjects affected / exposed <sup>[2]</sup><br>occurrences (all)  | 0 / 18 (0.00%)<br>0   | 1 / 17 (5.88%)<br>1   | 0 / 13 (0.00%)<br>0   |
| General disorders and administration site conditions<br>injection site reaction<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)   | 6 / 79 (7.59%)<br>34  | 3 / 90 (3.33%)<br>6   | 3 / 78 (3.85%)<br>4   |
| Eye disorders<br>ocular discomfort<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)  | 0 / 79 (0.00%)<br>0   | 0 / 90 (0.00%)<br>0   | 0 / 78 (0.00%)<br>0   |
| Reproductive system and breast disorders<br>adnexal torsion<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[3]</sup><br>occurrences (all)<br><br>menopausal symptoms<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[4]</sup><br>occurrences (all)<br><br>menstruation irregular<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[5]</sup><br>occurrences (all) | 0 / 18 (0.00%)<br>0<br><br><br><br>0 / 18 (0.00%)<br>0<br><br><br>0 / 18 (0.00%)<br>0 | 1 / 17 (5.88%)<br>1<br><br><br><br>0 / 17 (0.00%)<br>0<br><br><br>0 / 17 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0<br><br><br><br>0 / 13 (0.00%)<br>0<br><br><br>0 / 13 (0.00%)<br>0 |
| Gastrointestinal disorders<br>diarrhoea<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)   | 4 / 79 (5.06%)<br>4   | 4 / 90 (4.44%)<br>4   | 2 / 78 (2.56%)<br>2   |
| Musculoskeletal and connective tissue disorders<br>back pain<br>alternative dictionary used:<br>MedDRA 21.1  |   |   |   |



|   |                      |                     |                      |
|---|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 79 (1.27%)<br>1  | 1 / 90 (1.11%)<br>1 | 3 / 78 (3.85%)<br>3  |
| Infections and infestations<br>nasopharyngitis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all) | 7 / 79 (8.86%)<br>9  | 6 / 90 (6.67%)<br>7 | 8 / 78 (10.26%)<br>8 |
| upper respiratory tract infection<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)              | 8 / 79 (10.13%)<br>9 | 2 / 90 (2.22%)<br>3 | 4 / 78 (5.13%)<br>4  |
| vaginal infection<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[6]</sup><br>occurrences (all)               | 0 / 18 (0.00%)<br>0  | 1 / 17 (5.88%)<br>1 | 0 / 13 (0.00%)<br>0  |

| <b>Non-serious adverse events</b>   | PBO/IXE-extended<br>treatment period | ADA/PBO-washout<br>treatment period | ADA/PBO/IXE-<br>extended treatment<br>period |
|---|--------------------------------------|-------------------------------------|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 26 / 86 (30.23%)                     | 8 / 88 (9.09%)                      | 20 / 86 (23.26%)                             |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>uterine leiomyoma<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[2]</sup><br>occurrences (all) | 0 / 15 (0.00%)<br>0                  | 0 / 17 (0.00%)<br>0                 | 0 / 16 (0.00%)<br>0                          |
| General disorders and administration<br>site conditions<br>injection site reaction<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                         | 8 / 86 (9.30%)<br>53                 | 0 / 88 (0.00%)<br>0                 | 8 / 86 (9.30%)<br>24                         |
| Eye disorders<br>ocular discomfort<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)   | 0 / 86 (0.00%)<br>0                  | 0 / 88 (0.00%)<br>0                 | 0 / 86 (0.00%)<br>0                          |
| Reproductive system and breast  |                                      |                                     |  |

|   |                  |                |                |
|---|------------------|----------------|----------------|
| disorders                                       |                  |                |                |
| adnexal torsion                                 |                  |                |                |
| alternative dictionary used:<br>MedDRA 21.1     |                  |                |                |
| subjects affected / exposed <sup>[3]</sup>      | 0 / 15 (0.00%)   | 0 / 17 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0                | 0              | 0              |
| menopausal symptoms                             |                  |                |                |
| alternative dictionary used:<br>MedDRA 21.1     |                  |                |                |
| subjects affected / exposed <sup>[4]</sup>      | 0 / 15 (0.00%)   | 0 / 17 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0                | 0              | 0              |
| menstruation irregular                          |                  |                |                |
| alternative dictionary used:<br>MedDRA 21.1     |                  |                |                |
| subjects affected / exposed <sup>[5]</sup>      | 0 / 15 (0.00%)   | 0 / 17 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0                | 0              | 0              |
| Gastrointestinal disorders                      |                  |                |                |
| diarrhoea                                       |                  |                |                |
| alternative dictionary used:<br>MedDRA 21.1     |                  |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%)   | 0 / 88 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all)                               | 0                | 0              | 4              |
| Musculoskeletal and connective tissue disorders |                  |                |                |
| back pain                                       |                  |                |                |
| alternative dictionary used:<br>MedDRA 21.1     |                  |                |                |
| subjects affected / exposed                     | 0 / 86 (0.00%)   | 0 / 88 (0.00%) | 1 / 86 (1.16%) |
| occurrences (all)                               | 0                | 0              | 1              |
| Infections and infestations                     |                  |                |                |
| nasopharyngitis                                 |                  |                |                |
| alternative dictionary used:<br>MedDRA 21.1     |                  |                |                |
| subjects affected / exposed                     | 17 / 86 (19.77%) | 6 / 88 (6.82%) | 7 / 86 (8.14%) |
| occurrences (all)                               | 22               | 6              | 8              |
| upper respiratory tract infection               |                  |                |                |
| alternative dictionary used:<br>MedDRA 21.1     |                  |                |                |
| subjects affected / exposed                     | 4 / 86 (4.65%)   | 2 / 88 (2.27%) | 4 / 86 (4.65%) |
| occurrences (all)                               | 4                | 2              | 5              |
| vaginal infection                               |                  |                |                |
| alternative dictionary used:<br>MedDRA 21.1     |                  |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed <sup>[6]</sup> | 0 / 15 (0.00%) | 0 / 17 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                          | 0              | 0              | 0              |

| <b>Non-serious adverse events</b>                                   | IXE80Q2W-follow-up period | IXE80Q4W-follow-up period | PBO-follow-up period |
|---|---------------------------|---------------------------|----------------------|
| Total subjects affected by non-serious adverse events               |                           |                           |                      |
| subjects affected / exposed   | 2 / 24 (8.33%)            | 2 / 16 (12.50%)           | 1 / 1 (100.00%)      |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                           |                      |
| uterine leiomyoma   |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed <sup>[2]</sup>                          | 0 / 9 (0.00%)             | 0 / 3 (0.00%)             | 0 / 1 (0.00%)        |
| occurrences (all)   | 0                         | 0                         | 0                    |
| General disorders and administration site conditions                |                           |                           |                      |
| injection site reaction   |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed   | 0 / 24 (0.00%)            | 0 / 16 (0.00%)            | 0 / 1 (0.00%)        |
| occurrences (all)   | 0                         | 0                         | 0                    |
| Eye disorders   |                           |                           |                      |
| ocular discomfort   |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed   | 0 / 24 (0.00%)            | 0 / 16 (0.00%)            | 1 / 1 (100.00%)      |
| occurrences (all)   | 0                         | 0                         | 1                    |
| Reproductive system and breast disorders                            |                           |                           |                      |
| adnexal torsion   |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed <sup>[3]</sup>                          | 0 / 9 (0.00%)             | 0 / 3 (0.00%)             | 0 / 1 (0.00%)        |
| occurrences (all)   | 0                         | 0                         | 0                    |
| menopausal symptoms   |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed <sup>[4]</sup>                          | 0 / 9 (0.00%)             | 0 / 3 (0.00%)             | 1 / 1 (100.00%)      |
| occurrences (all)   | 0                         | 0                         | 1                    |
| menstruation irregular  |                           |                           |                      |
| alternative dictionary used: MedDRA 21.1                            |                           |                           |                      |
| subjects affected / exposed <sup>[5]</sup>                          | 0 / 9 (0.00%)             | 0 / 3 (0.00%)             | 0 / 1 (0.00%)        |
| occurrences (all)   | 0                         | 0                         | 0                    |
| Gastrointestinal disorders  |                           |                           |                      |

|  |  |  |  |
|--|--|--|--|
| diarrhoea<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)   | 1 / 24 (4.17%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0   |
| Musculoskeletal and connective tissue disorders<br>back pain<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)  | 0 / 24 (0.00%)<br>0  | 2 / 16 (12.50%)<br>2   | 0 / 1 (0.00%)<br>0   |
| Infections and infestations<br>nasopharyngitis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)<br><br>upper respiratory tract infection<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)<br><br>vaginal infection<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed <sup>[6]</sup><br>occurrences (all) | 0 / 24 (0.00%)<br>0<br><br>1 / 24 (4.17%)<br>1<br><br>0 / 9 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0 |

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific adverse event, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific adverse event, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific adverse event, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific adverse event, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific adverse event, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 23 December 2016 | To remove specific limitation of enrolling equal numbers of participants with elevated/non-elevated CRP such that all patients who meet protocol eligibility criteria can be enrolled independent of having elevated or nonelevated CRP. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported