# Clinical trial results:
# A Multicenter, Randomized, Double-Blind, Placebo-Controlled 16 Week Study Followed by Long Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in TNFi-Experienced Patients with Radiographic Axial Spondyloarthritis

## Summary

| | |
|---|---|
| EudraCT number | 2015-003937-84 |
| Trial protocol | GB FI NL DE ES PL FR IT |
| Global end of trial date | 03 May 2019 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 26 January 2020 |
| First version publication date | 26 January 2020 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | I1F-MC-RHBW |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02696798 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 16179 |

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:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 03 May 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 May 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy and safety of ixekizumab in tumor necrosis factor (TNF) inhibitor-experienced 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 | 12 April 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Puerto Rico: 7 |
| Country: Number of subjects enrolled | Argentina: 18 |
| Country: Number of subjects enrolled | United States: 40 |
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Country: Number of subjects enrolled | Spain: 14 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | Korea, Republic of: 34 |
| Country: Number of subjects enrolled | Netherlands: 3 |
| Country: Number of subjects enrolled | Finland: 5 |
| Country: Number of subjects enrolled | Brazil: 28 |
| Country: Number of subjects enrolled | Poland: 66 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Mexico: 39 |
| Country: Number of subjects enrolled | Israel: 16 |
| Country: Number of subjects enrolled | France: 17 |
| Country: Number of subjects enrolled | Germany: 1 |
| Worldwide total number of subjects | 316 |
| EEA total number of subjects | 128 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 292 |
| From 65 to 84 years | 24 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Blinded Treatment Dosing Period (Week 0 to Week 16), Extended Treatment Period (Week 16 to Week 52) followed by post-treatment follow-up period occurring from last treatment visit (week 52), or Early Termination Visit (ETV) up to a minimum of 12 weeks following that visit.

### Pre-assignment

Screening details:

Participants who completed study were eligible to enroll into a long-term study (I1F-MC-RHBY [2016-002634-69]) for up to 2 additional years. Participants who terminate study RHBW early or who do not enroll into Study RHBY will complete the Post-Treatment Follow-Up (PTFU) Period in study RHBW.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo (PBO) |

Arm description:

Participants received placebo every two weeks (Q2W) by subcutaneous (SC) injection during Week 0 to 16.

| | |
|---|---|
| Arm type | Placebo |
| 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 every two weeks (Q2W) by subcutaneous (SC) injection.

| | |
|---|---|
| **Arm title** | IXE80Q4W |

Arm description:

Participants received starting dose of 80 or 160 mg ixekizumab given SC at baseline followed by 80 mg ixekizumab given SC every four weeks (Q4W) up to week 16.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | IXE80Q4W |
| Investigational medicinal product code | |
| Other name | LY2439821; Ixekizumab |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

80 or 160 milligrams (mg) of ixekizumab given subcutaneously (SC).

| | |
|---|---|
| **Arm title** | IXE80Q2W |

Arm description:

Participants received starting dose of 80 or 160 milligrams (mg) ixekizumab given subcutaneously (SC) at baseline followed by 80 mg ixekizumab given SC every two weeks (Q2W) up to week 16.

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

| | |
|---|---|
| Investigational medicinal product name | IXE80Q2W |
| Investigational medicinal product code | |
| Other name | LY2439821; Ixekizumab |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

80 or 160 milligrams (mg) of ixekizumab given subcutaneously (SC).

| **Number of subjects in period 1** | Placebo (PBO) | IXE80Q4W | IXE80Q2W |
|---|---|---|---|
| Started | 104 | 114 | 98 |
| Completed | 93 | 99 | 90 |
| Not completed | 11 | 15 | 8 |
| Adverse event, serious fatal | - | - | 1 |
| Consent withdrawn by subject | 7 | 3 | 4 |
| Physician decision | - | 1 | - |
| Adverse event, non-fatal | 2 | 9 | 2 |
| Lost to follow-up | - | 1 | - |
| Lack of efficacy | 2 | 1 | 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 |
| **Arm title** | PBO/IXE |

Arm description:

Participants who received Placebo in blinded treatment period were re-randomized to receive ixekizumab 80 mg Q4W or 80 mg Q2W at a 1:1 ratio with starting dose of 160 mg.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | IXE |
| Investigational medicinal product code | |
| Other name | LY2439821; Ixekizumab |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants who received Placebo in blinded treatment period were re- randomized to receive ixekizumab 80 mg Q4W or 80 mg Q2W at a 1:1 ratio with starting dose of 160 mg.

| | |
|---|---|
| **Arm title** | IXE80Q4W/IXE80Q4W |

| | |
|---|---|
| Arm description: | |
| Participants received 80 mg ixekizumab given SC Q4W from week 16 to week 52. | |
| Arm type | Experimental |
| Investigational medicinal product name | IXE80Q4W/IXE80Q4W |
| Investigational medicinal product code | |
| Other name | LY2439821; Ixekizumab |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Participants received 80 mg ixekizumab given SC Q2W from week 16 to week 52. | |
| **Arm title** | IXE80Q2W/IXE80Q2W |
| Arm description: | |
| Participants received 80 mg ixekizumab given SC Q2W from week 16 to week 52. | |
| Arm type | Experimental |
| Investigational medicinal product name | IXE80Q2W/IXE80Q2W |
| Investigational medicinal product code | |
| Other name | LY2439821; Ixekizumab |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Participants received 80 mg ixekizumab given SC Q2W from week 16 to week 52. | |

| **Number of subjects in period 2[1]** | PBO/IXE | IXE80Q4W/IXE80Q4W | IXE80Q2W/IXE80Q2W |
|---|---|---|---|
| Started | 93 | 98 | 90 |
| Completed | 81 | 89 | 80 |
| Not completed | 12 | 9 | 10 |
| Consent withdrawn by subject | 3 | 2 | 3 |
| Physician decision | - | 1 | - |
| Adverse event, non-fatal | 1 | 4 | 5 |
| Lost to follow-up | 1 | - | - |
| Lack of efficacy | 7 | 2 | 2 |

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: 1 participant completed blinded treatment period and entered post-treatment followup period directly.

## Period 3

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

## Arms

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

| **Arm title** | Placebo |
|---|---|
| Arm description: | |
| Participants did not receive any intervention during Follow-up period | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| **Arm title** | IXE80Q4W |
| Arm description: | |
| Participants did not receive any intervention during Follow-up period | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| **Arm title** | IXE80Q2W |
| Arm description: | |
| Participants did not receive any intervention during Follow-up period | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| **Number of subjects in period 3**[2] | Placebo | IXE80Q4W | IXE80Q2W |
|---|---|---|---|
| Started | 5 | 34 | 22 |
| Completed | 0 | 8 | 3 |
| Not completed | 5 | 26 | 19 |
| Consent withdrawn by subject | 2 | 8 | 12 |
| Physician decision | - | 2 | - |
| Adverse event, non-fatal | 2 | 12 | 6 |
| No progressive improvement | - | 1 | - |
| Lost to follow-up | - | 1 | 1 |
| Lack of efficacy | 1 | 2 | - |

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 terminate RHBW early or who didn't enroll into RHBY entered Follow-Up Period.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo (PBO) |
| Reporting group description: | |
| Participants received placebo every two weeks (Q2W) by subcutaneous (SC) injection during Week 0 to 16. | |
| Reporting group title | IXE80Q4W |
| Reporting group description: | |
| Participants received starting dose of 80 or 160 mg ixekizumab given SC at baseline followed by 80 mg ixekizumab given SC every four weeks (Q4W) up to week 16. | |
| Reporting group title | IXE80Q2W |
| Reporting group description: | |
| Participants received starting dose of 80 or 160 milligrams (mg) ixekizumab given subcutaneously (SC) at baseline followed by 80 mg ixekizumab given SC every two weeks (Q2W) up to week 16. | |

| Reporting group values | Placebo (PBO) | IXE80Q4W | IXE80Q2W |
|---|---|---|---|
| Number of subjects | 104 | 114 | 98 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 46.6 | 47.4 | 44.2 |
| standard deviation | ± 12.72 | ± 13.36 | ± 10.79 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 17 | 23 | 23 |
| Male | 87 | 91 | 75 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 33 | 32 | 35 |
| Not Hispanic or Latino | 63 | 70 | 53 |
| Unknown or Not Reported | 8 | 12 | 10 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 4 | 4 | 4 |
| Asian | 13 | 14 | 13 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 2 | 2 |

| | | | |
|---|---|---|---|
| White | 85 | 91 | 78 |
| More than one race | 1 | 2 | 1 |
| Unknown or Not Reported | 0 | 1 | 0 |
| Region of Enrollment<br>Units: Subjects | | | |
| Puerto Rico | 1 | 2 | 4 |
| Argentina | 6 | 7 | 5 |
| United States | 14 | 14 | 12 |
| United Kingdom | 9 | 6 | 5 |
| Spain | 3 | 7 | 4 |
| Canada | 1 | 5 | 0 |
| South Korea | 12 | 11 | 11 |
| Netherlands | 1 | 2 | 0 |
| Finland | 0 | 3 | 2 |
| Brazil | 10 | 8 | 10 |
| Poland | 22 | 24 | 20 |
| Italy | 0 | 1 | 1 |
| Mexico | 13 | 13 | 13 |
| Israel | 5 | 5 | 6 |
| France | 7 | 5 | 5 |
| Germany | 0 | 1 | 0 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 316 | | |
| Age categorical<br>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<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 63 | | |
| Male | 253 | | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 100 | | |
| Not Hispanic or Latino | 186 | | |
| Unknown or Not Reported | 30 | | |
| Race (NIH/OMB)<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| American Indian or Alaska Native | 12 | | |
| Asian | 40 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 5 | | |
| White | 254 | | |
| More than one race | 4 | | |
| Unknown or Not Reported | 1 | | |
| Region of Enrollment<br>Units: Subjects | | | |
| Puerto Rico | 7 | | |
| Argentina | 18 | | |
| United States | 40 | | |
| United Kingdom | 20 | | |
| Spain | 14 | | |
| Canada | 6 | | |
| South Korea | 34 | | |
| Netherlands | 3 | | |
| Finland | 5 | | |
| Brazil | 28 | | |
| Poland | 66 | | |
| Italy | 2 | | |
| Mexico | 39 | | |
| Israel | 16 | | |
| France | 17 | | |
| Germany | 1 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo (PBO) |
| Reporting group description: | |
| Participants received placebo every two weeks (Q2W) by subcutaneous (SC) injection during Week 0 to 16. | |
| Reporting group title | IXE80Q4W |
| Reporting group description: | |
| Participants received starting dose of 80 or 160 mg ixekizumab given SC at baseline followed by 80 mg ixekizumab given SC every four weeks (Q4W) up to week 16. | |
| Reporting group title | IXE80Q2W |
| Reporting group description: | |
| Participants received starting dose of 80 or 160 milligrams (mg) ixekizumab given subcutaneously (SC) at baseline followed by 80 mg ixekizumab given SC every two weeks (Q2W) up to week 16. | |
| Reporting group title | PBO/IXE |
| Reporting group description: | |
| Participants who received Placebo in blinded treatment period were re-randomized to receive ixekizumab 80 mg Q4W or 80 mg Q2W at a 1:1 ratio with starting dose of 160 mg. | |
| Reporting group title | IXE80Q4W/IXE80Q4W |
| Reporting group description: | |
| Participants received 80 mg ixekizumab given SC Q4W from week 16 to week 52. | |
| Reporting group title | IXE80Q2W/IXE80Q2W |
| Reporting group description: | |
| Participants received 80 mg ixekizumab given SC Q2W from week 16 to week 52. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants did not receive any intervention during Follow-up period | |
| Reporting group title | IXE80Q4W |
| Reporting group description: | |
| Participants did not receive any intervention during Follow-up period | |
| Reporting group title | IXE80Q2W |
| Reporting group description: | |
| Participants did not receive any intervention during Follow-up period | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Participants received placebo every 2 weeks (Q2W) by subcutaneous injection. | |
| Subject analysis set title | 80 mg Q4W Ixekizumab |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Participants received starting dose of 80 or 160 mg ixekizumab by SC injection at baseline followed by 80 mg ixekizumab given SC every four weeks (Q4W). | |
| Subject analysis set title | 80 mg Q2W Ixekizumab |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Participants received starting dose of 80 or 160 mg ixekizumab given SC injection at baseline followed by 80 mg ixekizumab given SC every two weeks (Q2W) to week 16. | |
| Subject analysis set title | 80 mg Q4W Ixekizumab (Starting Dose 80 mg) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Participants received 80 mg of Ixekizumab every four weeks by subcutaneous injection. | |

| | |
|---|---|
| Subject analysis set title | 80 mg Q4W Ixekizumab (Starting Dose 160 mg) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Participants received 160 mg ixekizumab at baseline followed by 80 mg ixekizumab given SC every four weeks by subcutaneous injection.

| | |
|---|---|
| Subject analysis set title | 80 mg Q2W Ixekizumab (Starting Dose 80 mg) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Participants received 80 mg ixekizumab every two weeks by subcutaneous injection.

| | |
|---|---|
| Subject analysis set title | 80 mg Q2W Ixekizumab (Starting Dose 160 mg) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Participants received starting dose of 160 mg ixekizumab at baseline followed by 80 mg ixekizumab every two weeks by subcutaneous injection.

## 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 >= 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 domain.
1) Patient Global: How active was your Ankylosing spondylitis (AS) (on average during the last week? score ranges 0 (not active) to 10 (very active).
2) Spinal Pain: How much Pain of your spine due to AS? ranges 0 (no pain) to 10 (severe pain).
3) Bath Ankylosing Spondylitis Functional Index : Participant asked to rate the difficulty associated with 10 individual basic functional activities. Participant response was captured using Numeric Rating Scale (NRS) (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 (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 | Primary |

End point timeframe:

Week 16

| **End point values** | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 12.5 | 25.4 | 30.6 | |

## Statistical analyses

| **Statistical analysis title** | ASAS40 Response |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.17 |
| upper limit | 4.95 |

| **Statistical analysis title** | ASAS40 Response |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.48 |
| upper limit | 6.33 |

## 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 ≥20% improvement and an absolute improvement from baseline of ≥1 units (range 0 to 10) in ≥3 of 4 domains, and no worsening of ≥20% and ≥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 ranges 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 (BASFI): Participant asked to rate the difficulty associated with 10 individual basic functional activities. Participant response was captured using Numeric Rating Scale (NRS) (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 | Secondary |
|---|---|

End point timeframe:

Week 16

| End point values | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 29.8 | 48.2 | 46.9 | |

**Statistical analyses**

| Statistical analysis title | ASAS20 Response |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.26 |
| upper limit | 3.84 |

| Statistical analysis title | ASAS20 Response |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.013 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.16 |
| upper limit | 3.73 |

## 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 1) Total back pain, 2) Patient global, 3) Peripheral pain/swelling, 4) Duration of morning stiffness and 5) CRP in mg/L. The ASDAScrp is calculated with the equation: 0.121×total back pain+0.110×patient global+0.073×peripheral pain/swelling+0.058×duration of morning stiffness+0.579×Ln(CRP+1). (CRP is in mg/liter, the range of other variables is from (0 to 10); Ln represents the natural logarithm). Data from five variables combined to yield a score (0.6361 to no defined upper limit), where higher scores higher disease activity. Least square (LS) mean was determined by mixed-model repeated measures (MMRM) with treatment, geographic region, baseline CRP status, number of prior tumor necrosis factor inhibitor (TNFi), baseline value, visit,baseline value-byvisit,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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.11 (± 0.099) | -1.16 (± 0.094) | -1.13 (± 0.103) | |

**Statistical analyses**

| **Statistical analysis title** | ASDAS |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.32 |
| upper limit | -0.79 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.135 |

| **Statistical analysis title** | ASDAS |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | -0.75 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.14 |

## 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 (rad-axSpA): 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), with a higher score indicating more severe AS symptom. BASDAI50 represents an improvement of ≥50% of the BASDAI score from baseline.
APD: All randomized participants.

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

End point timeframe:

Week 16

| End point values | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 9.6 | 21.9 | 23.5 | |

### Statistical analyses

| Statistical analysis title | BASDAI50 |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.015 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.21 |
| upper limit | 5.84 |

| **Statistical analysis title** | BASDAI50 |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.29 |
| upper limit | 6.49 |

## Secondary: Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

| End point title | Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) |
|---|---|

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 (rad-axSpA): 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), with a higher score indicating more severe AS symptom. LSmean was determined by MMRM with factors for treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.92 (± 0.212) | -2.17 (± 0.202) | -2.09 (± 0.221) | |

**Statistical analyses**

| Statistical analysis title | BASDAI |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.81 |
| upper limit | -0.67 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.291 |

| Statistical analysis title | BASDAI |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.76 |
| upper limit | -0.57 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.301 |

## 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 participant's functional baseline and subsequent response to treatment. The BASFI is composed with 10 questions to assess the disease severity, including the first 8 questions regarding to functional anatomy related activities and the remaining 2 questions related to daily activities of AS participants. Participants respond to each question using an NRS scale (range 0 to 10). The BASFI score is the average of the 10 responses and has a possible minimum value of 0 and a possible maximum value of 10, with a higher score indicating worse function. LS mean was determined by MMRM with factors for treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.64 (± 0.215) | -1.69 (± 0.205) | -1.92 (± 0.225) | |

**Statistical analyses**

| **Statistical analysis title** | BASFI |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.63 |
| upper limit | -0.47 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.295 |

| **Statistical analysis title** | BASFI |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.89 |
| upper limit | -0.68 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.307 |

## Secondary: Percentage of Participants Achieving ASDAS Inactive Disease

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

End point description:

The ASDAS is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity (patient global), back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0.6361 to no defined upper limit), where higher the score worse the disease activity. 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 1.0 | 3.5 | 5.1 | |

### Statistical analyses

| Statistical analysis title | ASDAS Inactive Disease |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.242 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.41 |
| upper limit | 33.98 |

| **Statistical analysis title** | ASDAS Inactive Disease |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.127 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 5.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 47.54 |

## Secondary: Percentage of Participants Achieving ASDAS <2.1

| End point title | Percentage of Participants Achieving ASDAS <2.1 |
|---|---|

End point description:

The ASDAS is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity (patient global), back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0.6361 to no defined upper limit), where higher the score worse the disease activity. ASDAS <2.1 defines moderate disease activity.
APD: All randomized participants.

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

End point timeframe:

Week 16

| End point values | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 4.8 | 17.5 | 16.3 | |

**Statistical analyses**

| Statistical analysis title | ASDAS <2.1 |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.5 |
| upper limit | 11.86 |

| Statistical analysis title | ASDAS <2.1 |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.55 |
| upper limit | 13.18 |

## 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 determined by MMRM with factors for treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| SF-36 MCS | 2.7410 (± 0.9452) | 3.5099 (± 0.9074) | 3.6514 (± 0.9921) | |
| SF-36 PCS | 1.3638 (± 0.8146) | 6.5785 (± 0.7763) | 6.1223 (± 0.8465) | |

**Statistical analyses**

| **Statistical analysis title** | SF-36 MCS |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.55 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.7689 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7629 |
| upper limit | 3.3007 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.2863 |

| **Statistical analysis title** | SF-36 MCS |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.495 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.9104 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7151 |
| upper limit | 3.536 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.3338 |

| **Statistical analysis title** | SF-36 PCS |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 5.2147 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.0204 |
| upper limit | 7.409 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.1149 |

| **Statistical analysis title** | SF-36 PCS |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 4.7585 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.494 |
| upper limit | 7.023 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.1505 |

## 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:

The ASAS Health Index (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 1 question that the patient needs to respond to with either "I agree" (score 1) or "I do not agree (score 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. LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.89 (± 0.338) | -1.92 (± 0.322) | -1.58 (± 0.352) | |

### Statistical analyses

| Statistical analysis title | ASAS HI |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.026 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.94 |
| upper limit | -0.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.46 |

| **Statistical analysis title** | ASAS HI |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.149 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.63 |
| upper limit | 0.25 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.477 |

## 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 study used MRI with fat-saturating techniques such as short tau inversion recovery (STIR) to look for the presence of bone marrow edema. The Berlin modification of Ankylosing Spondylitis spine MRI score for activity (ASspiMRI) scoring technique assesses inflammation in each of the 23 disco-vertebral units (DVU) of the spine (from C2 to S1), capturing 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 that 50% of DVU)]. The composite score ranges from 0 to 69, with higher scores reflecting worse disease.LS mean was determined by analysis of covariance (ANCOVA) with treatment, geographic region, baseline CRP status, number of prior TNF inhibitors used and baseline value as fixed factors.
APD: All randomized participants with baseline and week 16 ASSpiMRI score.

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

End point timeframe:

Baseline, Week 16

| **End point values** | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 46 | 49 | 45 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 1.03 (± 0.379) | -0.92 (± 0.373) | -1.14 (± 0.414) | |

**Statistical analyses**

| **Statistical analysis title** | ASSpiMRI score |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | -0.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.512 |

| **Statistical analysis title** | ASSpiMRI score |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -2.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | -1.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.534 |

## 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 (DVU) of the spine (from C2 to S1) were scored for bone marrow edema. A single DVU has 18 scoring units, and each has score of 0 or 1, bringing the maximum total score to 414, the sum ranges from 0 to 414 with higher scores reflecting worse disease. Scoring was performed by central readers. LS mean was determined by ANCOVA with factors for treatment, geographic region, baseline CRP status, number of prior TNF inhibitors used and baseline value.
APD: All randomized participants with baseline and week 16 SPARCC MRI score.

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

End point timeframe:

Baseline, Week 16

| **End point values** | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 46 | 49 | 45 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 3.29 (± 1.402) | -2.99 (± 1.384) | -3.97 (± 1.534) | |

**Statistical analyses**

| **Statistical analysis title** | SPARCC score |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -6.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10 |
| upper limit | -2.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.896 |

| **Statistical analysis title** | SPARCC score |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -7.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.2 |
| upper limit | -3.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.978 |

## 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 was measured with a high sensitivity assay at the central laboratory to help assess the effect of ixekizumab on disease activity. High sensitivity CRP is a sensitive laboratory assay for serum levels of C-Reactive Protein, which is a biomarker of inflammation. LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: milligram per liter (mg/L) | | | | |
| least squares mean (standard error) | 9.719 (± 2.7383) | -11.096 (± 2.6190) | -8.121 (± 2.8829) | |

## Statistical analyses

| Statistical analysis title | High Sensitivity C-Reactive Protein |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -20.816 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.187 |
| upper limit | -13.444 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.7463 |

| **Statistical analysis title** | High Sensitivity C-Reactive Protein |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -17.841 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.518 |
| upper limit | -10.163 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.9018 |

## Secondary: Change from Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI)

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

End point description:

BASMI is a combined index comprising of 5 clinical measurements of spinal mobility in patients with radaxSpA.
1) Lateral Spinal Flexion
2) Tragus-to-wall distance
3) Lumbar Flexion (modified Schober)
4) Maximal intermalleolar distance and
5) Cervical rotation. The BASMI linear result is the average of the 5 assessments and ranges from 0 to 10. The higher the BASMI score the more severe the patient’s limitation of movement due to their AS.
LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.046 (± 0.0939) | -0.349 (± 0.0897) | -0.217 (± 0.0981) | |

**Statistical analyses**

| **Statistical analysis title** | BASMI |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.018 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.304 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.555 |
| upper limit | -0.053 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1275 |

| **Statistical analysis title** | BASMI |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.194 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.172 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.431 |
| upper limit | 0.088 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1319 |

## Secondary: Change from Baseline in Chest Expansion

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

End point description:

Chest expansion is the difference, in centimeter (cm), between the circumference of the chest in maximal inspiration and maximal expiration. While patients have their hands resting on or behind the head, the assessor will measure the chest encircled length by centimeter (cm) at the fourth intercostal level anteriorly. Two tries were recorded. The better measurement (larger difference) of 2 tries (in centimeters) was used for analyses. LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: centimeter(cm) | | | | |
| least squares mean (standard error) | 0.04 (± 0.644) | 1.27 (± 0.618) | 0.27 (± 0.655) | |

### Statistical analyses

| Statistical analysis title | Chest Expansion |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 2.99 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.893 |

| Statistical analysis title | Chest Expansion |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.57 |
| upper limit | 2.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.916 |

## 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. LS mean was determined by MMRM with factors for treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: cm | | | | |
| least squares mean (standard error) | 0.35 (± 0.384) | 0.03 (± 0.365) | -0.65 (± 0.399) | |

## Statistical analyses

| Statistical analysis title | Occiput to Wall Distance |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.547 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.34 |
| upper limit | 0.71 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.521 |

| **Statistical analysis title** | Occiput to Wall Distance |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.064 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.06 |
| upper limit | 0.06 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.538 |

## 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. LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, 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

| End point values | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 69 | 82 | 74 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -1.9 (± 0.43) | -1.8 (± 0.40) | -2.2 (± 0.42) | |

**Statistical analyses**

| Statistical analysis title | MASES |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.861 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 1.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.58 |

| Statistical analysis title | MASES |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.626 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 0.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.59 |

## Secondary: Change from Baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Score

| End point title | Change from Baseline in Spondyloarthritis Research Consortium of Canada (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. LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction as fixed factors.
APD: All randomized participants with baseline SPARCC Enthesitis score>0.

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

End point timeframe:

Baseline, Week 16

| **End point values** | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 60 | 78 | 64 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -1.9 (± 0.44) | -2.3 (± 0.40) | -1.8 (± 0.45) | |

### Statistical analyses

| **Statistical analysis title** | SPARCC- Enthesitis Score |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 138 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.504 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 0.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.59 |

| Statistical analysis title | SPARCC- Enthesitis Score |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.86 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 1.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.62 |

**Secondary: Change from Baseline in Severity of Peripheral Arthritis by Tender Joint Count (TJC) Scores**

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

End point description:

The number of tender and painful joints was determined by examination of 46 joints (23 joints on each side of the body). The 46 joints were assessed and classified as tender or not tender. Sum of all joints checked to be tender/painful divided by number of evaluable joints which was multiplied by 46 to obtain TJC score. The scores ranges from 0 (no tender/painful joints) to 46 (all joints tender/painful). LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction.
APD: All randomized participants with baseline TJC>0.

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

End point timeframe:

Baseline, Week 16

| End point values | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 65 | 85 | 69 | |
| Units: Tender Joint Count | | | | |
| least squares mean (standard error) | -3.9 (± 0.79) | -4.8 (± 0.69) | -5.0 (± 0.79) | |

**Statistical analyses**

| Statistical analysis title | TJC Scores |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 150 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.362 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | 1.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.03 |

| Statistical analysis title | TJC Scores |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 134 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.303 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | 1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.08 |

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

| End point title | Change from Baseline in Severity of Peripheral Arthritis by Swollen Joint Count (SJC) Scores |
|---|---|

End point description:

The number of swollen joints was determined by examination of 44 joints (22 joints on each side of the body). The 44 joints were assessed and classified as swollen or not swollen. Sum of all joints checked to be swollen divided by number of evaluable joints which was multiplied by 44 to obtain SJC score. The SJC score ranges from 0 (no swollen joints) to 44 (all joints swollen). LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, baseline value, visit, baseline value-by-visit, and treatment-by-visit interaction.
APD: All randomized participants with baseline SJC>0.

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

End point timeframe:
Baseline, Week 16

| **End point values** | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 45 | 48 | 44 | |
| Units: Swollen Joint Count | | | | |
| least squares mean (standard error) | -2.4 (± 0.51) | -2.6 (± 0.49) | -3.0 (± 0.54) | |

**Statistical analyses**

| **Statistical analysis title** | SJC Scores |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 93 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.813 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 1.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7 |

| **Statistical analysis title** | SJC Scores |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.41 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2 |
| upper limit | 0.8 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.71 |

## Secondary: Percentage of Participants with Anterior Uveitis

| | |
|---|---|
| End point title | Percentage of Participants with Anterior Uveitis |

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:

Week 16

| End point values | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 0 | 1.8 | 3.1 | |

### Statistical analyses

| Statistical analysis title | Anterior Uveitis |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.499 |
| Method | Fisher exact |
| Parameter estimate | Incidence Rate |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 4.2 |

| Statistical analysis title | Anterior Uveitis |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.112 |
| Method | Fisher exact |
| Parameter estimate | Incidence Rate |
| Point estimate | 3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 6.5 |

## 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 1 number that describes their worst level of fatigue during the previous 24 hours. LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.7 (± 0.24) | -2.0 (± 0.23) | -1.7 (± 0.25) | |

### Statistical analyses

| Statistical analysis title | Fatigue NRS Score |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.2 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | -0.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.33 |

| **Statistical analysis title** | Fatigue NRS Score |
|---|---|
| Comparison groups | 80 mg Q2W Ixekizumab v Placebo |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | -0.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.34 |

## 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 Jenkins Sleep Evaluation Questionnaire (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. Patients report the numbers 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. LS mean was determined by MMRM with treatment, geographic region, baseline CRP status, number of prior TNFi, 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 | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 114 | 98 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -1.8 (± 0.50) | -3.0 (± 0.48) | -2.4 (± 0.52) | |

**Statistical analyses**

| Statistical analysis title | JSEQ |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.088 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 0.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.68 |

| Statistical analysis title | JSEQ |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.366 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2 |
| upper limit | 0.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7 |

**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, with higher scores indicating greater impairment and less productivity. LS mean was determined by ANCOVA with treatment, geographic region, baseline CRP status, number of prior TNFi and baseline value as fixed factors.
APD: All randomized participants with baseline and week 16 WPAI-SpA score.

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

End point timeframe:

Baseline, Week 16

| **End point values** | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 99[1] | 112[2] | 96[3] | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Overall Work Impairment Score | -9.84 (± 3.733) | -20.97 (± 4.016) | -23.50 (± 4.225) | |
| Percentage of Activity Impairment | -10.1 (± 2.60) | -16.5 (± 2.44) | -18.4 (± 2.74) | |

Notes:

[1] - N=54 for Overall Work Impairment Score

[2] - N= 44 for Overall Work Impairment Score

[3] - N= 43 for Overall Work Impairment Score

## Statistical analyses

| **Statistical analysis title** | Overall Work Impairment Score |
|---|---|

Statistical analysis description:

Subjects in this analysis: 98

| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
|---|---|
| Number of subjects included in analysis | 211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.038 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -11.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.65 |
| upper limit | -0.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.323 |

| **Statistical analysis title** | Overall Work Impairment Score |
|---|---|
| Statistical analysis description:<br>Subjects in this analysis: 97 | |
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |
| Number of subjects included in analysis | 195 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.012 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -13.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.23 |
| upper limit | -3.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.341 |

| **Statistical analysis title** | Percentage of Activity Impairment |
|---|---|
| Comparison groups | Placebo v 80 mg Q4W Ixekizumab |
| Number of subjects included in analysis | 211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.071 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -6.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.2 |
| upper limit | 0.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.5 |

| **Statistical analysis title** | Percentage of Activity Impairment |
|---|---|
| Comparison groups | Placebo v 80 mg Q2W Ixekizumab |

| | |
|---|---|
| Number of subjects included in analysis | 195 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.024 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference (Final Values) |
| Point estimate | -8.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.5 |
| upper limit | -1.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.65 |

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

| | |
|---|---|
| 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). For NSAID equivalent scoring system, range is from 0 to 100, higher the score greated the NSAID intake. ASAS-NSAID score= (equivalent NSAID score) x (days of intake during PI) x (days per week)/(PI in days).
APD: Participants from extended treatment period who had NSAID Intake at baseline.

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

End point timeframe:

Baseline, Week 52

| End point values | PBO/IXE | IXE80Q4W/IXE 80Q4W | IXE80Q2W/IXE 80Q2W | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 69 | 71 | 58 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -9.84 (± 34.435) | -5.52 (± 19.553) | -2.33 (± 24.019) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Anti-Ixekizumab Antibodies

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

End point description:

A TE-ADA positive patient is defined as: a) a patient with a >= 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 >= 1:10. Percentage of participants with treatment-emergent positive anti-ixekizumab antibodies was summarized by treatment group. Percentage was calculated based on the number of evaluable participants and was calculated by number of participants with treatment-emergent positive anti-ixekizumab antibodies / number of evaluable participants * 100%.
APD: All randomized participants.

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

End point timeframe:

Week 16

| **End point values** | Placebo | 80 mg Q4W Ixekizumab | 80 mg Q2W Ixekizumab | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 104 | 113 | 98 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 2.9 | 7.1 | 4.1 | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Pharmacokinetics (PK): Trough Ixekizumab Concentration at Steady State (Ctrough ss)**

| End point title | Pharmacokinetics (PK): Trough Ixekizumab Concentration at Steady State (Ctrough ss) |
|---|---|

End point description:

Pharmacokinetics (PK): Steady-state trough serum concentration of Ixekizumab at week 16.
APD: All randomized participants who received study drug and have evaluable PK data.

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

End point timeframe:

Predose, Week 1, 2, 4, 8, 12 and Week 16

| **End point values** | 80 mg Q4W Ixekizumab (Starting Dose 80 mg) | 80 mg Q4W Ixekizumab (Starting Dose 160 mg) | 80 mg Q2W Ixekizumab (Starting Dose 80 mg) | 80 mg Q2W Ixekizumab (Starting Dose 160 mg) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 54 | 48 | 50 |
| Units: Microgram/milliliters (µg/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Week 16 | 2.10 (± 106) | 2.47 (± 101) | 6.27 (± 158) | 8.52 (± 50) |

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Blinded Treatment, Extended Treatment and Follow-Up Periods | |
| Adverse event reporting additional description: | |
| I1F-MC-RHBW | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.0 |

| Reporting groups | |
|---|---|
| Reporting group title | IXE80Q2W-blinded treatment period |
| Reporting group description: - | |
| Reporting group title | IXE80Q4W-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 | IXE80Q4W/IXE80Q4W-extended treatment period |
| Reporting group description: - | |
| Reporting group title | IXE80Q2W-follow-up period |
| Reporting group description: - | |
| Reporting group title | PBO/IXE-extended treatment 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 | IXE80Q2W-blinded treatment period | IXE80Q4W-blinded treatment period | PBO-blinded treatment period |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 98 (3.06%) | 4 / 114 (3.51%) | 5 / 104 (4.81%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| acute promyelocytic leukaemia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |

| | | | |
|---|---|---|---|
| lung adenocarcinoma | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| Vascular disorders | | | |
| vasculitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| Psychiatric disorders | | | |
| completed suicide | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 114 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| depression | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| blood creatine phosphokinase increased | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 114 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| femur fracture | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 1 / 104 (0.96%) |
| 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 | | | |
| acute myocardial infarction | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| atrial tachycardia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| bradycardia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 | | | |
| drop attacks | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |

| | | | |
|---|---|---|---|
| loss of consciousness | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| meralgia paraesthetica | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| syncope | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 | | | |
| colitis ulcerative | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| crohn's disease | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 114 (0.88%) | 0 / 104 (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 |
| inguinal hernia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| acute kidney injury | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 retention | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| fracture pain | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 114 (0.88%) | 0 / 104 (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 |
| osteoarthritis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 | | | |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| peritonitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 114 (0.88%) | 0 / 104 (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 |
| pharyngitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 114 (0.88%) | 0 / 104 (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 | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| sinusitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (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 |
| Metabolism and nutrition disorders | | | |
| hyperkalaemia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | IXE80Q2W/IXE80Q2W-extended treatment period | IXE80Q4W/IXE80Q4W-extended treatment period | IXE80Q2W-follow-up period |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 2 / 98 (2.04%) | 1 / 22 (4.55%) |
| 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) | | | |
| acute promyelocytic leukaemia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| lung adenocarcinoma | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| vasculitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| Psychiatric disorders | | | |
| completed suicide | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| depression | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 | | | |
| femur fracture | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 | | | |
| acute myocardial infarction | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| atrial tachycardia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| bradycardia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 98 (1.02%) | 0 / 22 (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 |
| Nervous system disorders | | | |
| drop attacks | | | |

| | | | |
|---|---|---|---|
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| loss of consciousness | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| meralgia paraesthetica | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| syncope | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 | | | |
| colitis ulcerative | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| crohn's disease | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| inguinal hernia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 | | | |
| acute kidney injury | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 98 (1.02%) | 0 / 22 (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 |
| urinary retention | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 98 (1.02%) | 0 / 22 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| arthritis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| fracture pain | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 | | | |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 98 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| peritonitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| pharyngitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| sinusitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 0 / 98 (0.00%) | 0 / 22 (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 |
| Metabolism and nutrition disorders | | | |
| hyperkalaemia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 90 (0.00%) | 1 / 98 (1.02%) | 0 / 22 (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 |

| **Serious adverse events** | PBO/IXE-extended treatment period | IXE80Q4W-follow-up period | PBO-follow-up period |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | 2 / 34 (5.88%) | 0 / 5 (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) | | | |
| acute promyelocytic leukaemia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 34 (2.94%) | 0 / 5 (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 |
| lung adenocarcinoma | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| Vascular disorders | | | |
| vasculitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 34 (2.94%) | 0 / 5 (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 |
| Psychiatric disorders | | | |
| completed suicide | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| depression | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 | | | |
| femur fracture | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 | | | |
| acute myocardial infarction | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| atrial tachycardia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| bradycardia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 | | | |
| drop attacks | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| loss of consciousness | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 34 (2.94%) | 0 / 5 (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 |
| meralgia paraesthetica | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| syncope | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 34 (2.94%) | 0 / 5 (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 | | | |
| colitis ulcerative | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| crohn's disease | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| inguinal hernia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| Renal and urinary disorders | | | |
| acute kidney injury | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 retention | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| fracture pain | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| Infections and infestations | | | |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| peritonitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| pharyngitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| sinusitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 0 / 5 (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 |
| Metabolism and nutrition disorders | | | |
| hyperkalaemia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (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 |

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

| **Non-serious adverse events** | IXE80Q2W-blinded treatment period | IXE80Q4W-blinded treatment period | PBO-blinded treatment period |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 98 (25.51%) | 25 / 114 (21.93%) | 12 / 104 (11.54%) |
| Investigations | | | |
| blood triglycerides increased | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 0 / 114 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| injection site reaction | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 8 / 98 (8.16%) | 3 / 114 (2.63%) | 1 / 104 (0.96%) |
| occurrences (all) | 21 | 5 | 1 |
| Gastrointestinal disorders | | | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 4 / 98 (4.08%) | 6 / 114 (5.26%) | 0 / 104 (0.00%) |
| occurrences (all) | 4 | 6 | 0 |
| Reproductive system and breast disorders | | | |
| vulvovaginal burning sensation | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed[1] | 0 / 23 (0.00%) | 0 / 23 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| vulvovaginal dryness | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed[2] | 0 / 23 (0.00%) | 0 / 23 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| arthralgia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 3 / 98 (3.06%) | 7 / 114 (6.14%) | 4 / 104 (3.85%) |
| occurrences (all) | 3 | 8 | 4 |
| back pain | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 3 / 98 (3.06%) | 1 / 114 (0.88%) | 2 / 104 (1.92%) |
| occurrences (all) | 3 | 1 | 2 |
| Infections and infestations | | | |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 4 / 98 (4.08%) | 5 / 114 (4.39%) | 2 / 104 (1.92%) |
| occurrences (all) | 4 | 5 | 2 |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 4 / 98 (4.08%) | 9 / 114 (7.89%) | 3 / 104 (2.88%) |
| occurrences (all) | 4 | 12 | 3 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 2 / 98 (2.04%) | 0 / 114 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| vulvovaginal candidiasis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed[3] | 0 / 23 (0.00%) | 0 / 23 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | IXE80Q2W/IXE80Q2W-extended treatment period | IXE80Q4W/IXE80Q4W-extended treatment period | IXE80Q2W-follow-up period |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 26 / 90 (28.89%) | 19 / 98 (19.39%) | 1 / 22 (4.55%) |
| Investigations | | | |
| blood triglycerides increased | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 90 (1.11%) | 0 / 98 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| injection site reaction<br>alternative dictionary used: MedDRA 22.0<br>subjects affected / exposed<br>occurrences (all) | 5 / 90 (5.56%)<br>14 | 2 / 98 (2.04%)<br>2 | 0 / 22 (0.00%)<br>0 |
| Gastrointestinal disorders<br>diarrhoea<br>alternative dictionary used: MedDRA 22.0<br>subjects affected / exposed<br>occurrences (all) | 2 / 90 (2.22%)<br>2 | 1 / 98 (1.02%)<br>1 | 0 / 22 (0.00%)<br>0 |
| Reproductive system and breast disorders<br>vulvovaginal burning sensation<br>alternative dictionary used: MedDRA 22.0<br>subjects affected / exposed[1]<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | 1 / 17 (5.88%)<br>1 | 0 / 4 (0.00%)<br>0 |
| vulvovaginal dryness<br>alternative dictionary used: MedDRA 22.0<br>subjects affected / exposed[2]<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | 1 / 17 (5.88%)<br>1 | 0 / 4 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>arthralgia<br>alternative dictionary used: MedDRA 22.0<br>subjects affected / exposed<br>occurrences (all) | 2 / 90 (2.22%)<br>2 | 4 / 98 (4.08%)<br>4 | 1 / 22 (4.55%)<br>2 |
| back pain<br>alternative dictionary used: MedDRA 22.0<br>subjects affected / exposed<br>occurrences (all) | 5 / 90 (5.56%)<br>5 | 6 / 98 (6.12%)<br>8 | 0 / 22 (0.00%)<br>0 |
| Infections and infestations<br>nasopharyngitis<br>alternative dictionary used: MedDRA 22.0<br>subjects affected / exposed<br>occurrences (all) | 4 / 90 (4.44%)<br>4 | 3 / 98 (3.06%)<br>3 | 0 / 22 (0.00%)<br>0 |
| upper respiratory tract infection<br>alternative dictionary used: MedDRA 22.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 90 (8.89%) | 4 / 98 (4.08%) | 0 / 22 (0.00%) |
| occurrences (all) | 10 | 4 | 0 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 5 / 90 (5.56%) | 2 / 98 (2.04%) | 0 / 22 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| vulvovaginal candidiasis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed[3] | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | PBO/IXE-extended treatment period | IXE80Q4W-follow-up period | PBO-follow-up period |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 93 (20.43%) | 3 / 34 (8.82%) | 1 / 5 (20.00%) |
| Investigations | | | |
| blood triglycerides increased | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 34 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| General disorders and administration site conditions | | | |
| injection site reaction | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 34 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Gastrointestinal disorders | | | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 0 / 34 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| vulvovaginal burning sensation | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed[1] | 0 / 16 (0.00%) | 0 / 9 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| vulvovaginal dryness | | | |

| | | | |
|---|---|---|---|
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed[2] | 0 / 16 (0.00%) | 0 / 9 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| arthralgia | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | 1 / 34 (2.94%) | 0 / 5 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| back pain | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 34 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 2 / 34 (5.88%) | 0 / 5 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | 0 / 34 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed | 2 / 93 (2.15%) | 0 / 34 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| vulvovaginal candidiasis | | | |
| alternative dictionary used: MedDRA 22.0 | | | |
| subjects affected / exposed[3] | 1 / 16 (6.25%) | 0 / 9 (0.00%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

Notes:

[1] - 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: This event is gender specific, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.
[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: This event is gender specific, 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: This event is gender specific, 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? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported