# Clinical trial results:
# A Randomized, Double-blind, Multi-dose, Placebo-controlled Phase 2/3 Study to Evaluate the Efficacy and Safety of Fasinumab in Patients With Moderate to Severe Chronic Low Back Pain

## Summary

| | |
|---|---|
| EudraCT number | 2015-003782-28 |
| Trial protocol | DK CZ PL HU |
| Global end of trial date | 12 September 2017 |

### Results information

| | |
|---|---|
| Result version number | v3 (current) |
| This version publication date | 24 June 2020 |
| First version publication date | 30 September 2018 |
| Version creation reason | |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | R475-PN-1524 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02620020 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Regeneron Pharmaceuticals, Inc. |
| Sponsor organisation address | 777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591 |
| Public contact | Clinical Trial Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com |
| Scientific contact | Clinical Trial Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 17 August 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 12 September 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of fasinumab compared to placebo in reducing low back pain (LBP) as measured by the change from baseline to Week 16 in the average daily low back pain intensity (LBPI) numeric rating scale (NRS) score.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 25 January 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 92 |
| Country: Number of subjects enrolled | Czech Republic: 63 |
| Country: Number of subjects enrolled | Denmark: 76 |
| Country: Number of subjects enrolled | Estonia: 12 |
| Country: Number of subjects enrolled | Hungary: 31 |
| Country: Number of subjects enrolled | United States: 286 |
| Country: Number of subjects enrolled | Canada: 3 |
| Worldwide total number of subjects | 563 |
| EEA total number of subjects | 274 |

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) | 414 |
| From 65 to 84 years | 147 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 105 sites in the US, CA & EU between 26 Jan 2016 & 13 Sep 2017. Of 1,783 subjects, 563 were randomized in 1:1:1:1 ratio to 1 of 4 treatment groups stratified by baseline LBPI, NRS score (<7, ≥7), duration of chronic LBP (<5 yrs, ≥5yrs) & maximum Kellgren-Lawrence (K-L) score (≤2, >2) at any knee or hip joint at screening.

### Pre-assignment

Screening details:

The study consisted of a screening period of up to 30 days & a 7-day pre-randomization period during which pain medication, except study-provided rescue medication, was discontinued. Confirmation of no exclusionary findings on joint on which imaging was performed during screening must have been received before a subject could be randomized.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo SC Q4W and Placebo IV Q8W |

Arm description:

Subjects randomized to the matching placebo subcutaneously (SC) every four weeks (Q4W) arm received SC placebo in a manner similar to the SC loading dose of the active groups (placebo loading dose) on Day 1 and then an SC injection of placebo at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo intravenously (IV) every 8 weeks (Q8W) was received on Day 1 and at Week 8.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo IV (Matching to Fasinumab) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received IV infusion of placebo (matching to fasinumab) on Day 1 and at Week 8.

| | |
|---|---|
| Investigational medicinal product name | Placebo SC (Matching to Fasinumab) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subject received SC injection of placebo (matching to fasinumab) on Day 1, and at Week 4, 8, 12.

| | |
|---|---|
| **Arm title** | Fasinumab 6 mg SC Q4W and Placebo IV Q8W |

Arm description:

Subjects randomized to the fasinumab 6 mg SC Q4W arm received fasinumab 12 mg SC on Day 1 (loading dose) and then 6 mg SC (planned maintenance dose) at Weeks 4, 8, and 12 for a total of 4 doses. Matching placebo was received via intravenous (IV) infusion Q8W on Day 1 and at Week 8.

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

| | |
|---|---|
| Investigational medicinal product name | Fasinumab |
| Investigational medicinal product code | REGN475 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subject received SC injection of fasinumab on Day 1, and at Week 4, 8, 12.

| | |
|---|---|
| Investigational medicinal product name | Placebo (Matching to Fasinumab) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received IV infusion of placebo (matching to fasinumab) on Day 1 and at Week 8.

| | |
|---|---|
| **Arm title** | Fasinumab 9 mg SC Q4W and Placebo IV Q8W |

Arm description:

Subjects randomized to the fasinumab 9 mg SC Q4W arm received 18 mg SC on day 1 (loading dose) and then 9 mg SC (planned maintenance dose) at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Fasinumab |
| Investigational medicinal product code | REGN475 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subject received SC injection of fasinumab on Day 1, and at Week 4, 8, 12.

| | |
|---|---|
| Investigational medicinal product name | Placebo (Matching to Fasinumab) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received IV infusion of placebo (matching to fasinumab) on Day 1 and at Week 8.

| | |
|---|---|
| **Arm title** | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |

Arm description:

Subjects randomized to the fasinumab 9 mg IV Q8W arm received IV infusions of fasinumab 9 mg on Day 1 and Week 8, for a total of 2 doses. Matching placebo SC Q4W was received on day 1 and at weeks 4, 8, and 12.

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

Dosage and administration details:

Subject received SC injection of placebo (matching to fasinumab) on Day 1, and at Week 4, 8, 12.

| | |
|---|---|
| Investigational medicinal product name | Fasinumab |
| Investigational medicinal product code | REGN475 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subject received IV infusion of fasinumab on Day 1, and at Week 8.

| **Number of subjects in period 1** | Placebo SC Q4W and Placebo IV Q8W | Fasinumab 6 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg SC Q4W and Placebo IV Q8W |
|---|---|---|---|
| Started | 141 | 141 | 140 |
| Modified Intent to Treat Set (mITT) | 140 | 139 | 139 |
| Completed | 97 | 106 | 115 |
| Not completed | 44 | 35 | 25 |
| Physician decision | 7 | 4 | 3 |
| Consent withdrawn by subject | 20 | 16 | 17 |
| Death | - | 1 | - |
| Adverse event | 8 | 4 | 3 |
| Lost to follow-up | 4 | 8 | 1 |
| Protocol deviation | 5 | 2 | 1 |

| **Number of subjects in period 1** | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |
|---|---|
| Started | 141 |
| Modified Intent to Treat Set (mITT) | 140 |
| Completed | 115 |
| Not completed | 26 |
| Physician decision | 4 |
| Consent withdrawn by subject | 12 |
| Death | - |
| Adverse event | 5 |
| Lost to follow-up | 4 |
| Protocol deviation | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo SC Q4W and Placebo IV Q8W |
| Reporting group description: | |
| Subjects randomized to the matching placebo subcutaneously (SC) every four weeks (Q4W) arm received SC placebo in a manner similar to the SC loading dose of the active groups (placebo loading dose) on Day 1 and then an SC injection of placebo at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo intravenously (IV) every 8 weeks (Q8W) was received on Day 1 and at Week 8. | |
| Reporting group title | Fasinumab 6 mg SC Q4W and Placebo IV Q8W |
| Reporting group description: | |
| Subjects randomized to the fasinumab 6 mg SC Q4W arm received fasinumab 12 mg SC on Day 1 (loading dose) and then 6 mg SC (planned maintenance dose) at Weeks 4, 8, and 12 for a total of 4 doses. Matching placebo was received via intravenous (IV) infusion Q8W on Day 1 and at Week 8. | |
| Reporting group title | Fasinumab 9 mg SC Q4W and Placebo IV Q8W |
| Reporting group description: | |
| Subjects randomized to the fasinumab 9 mg SC Q4W arm received 18 mg SC on day 1 (loading dose) and then 9 mg SC (planned maintenance dose) at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8. | |
| Reporting group title | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |
| Reporting group description: | |
| Subjects randomized to the fasinumab 9 mg IV Q8W arm received IV infusions of fasinumab 9 mg on Day 1 and Week 8, for a total of 2 doses. Matching placebo SC Q4W was received on day 1 and at weeks 4, 8, and 12. | |

| **Reporting group values** | Placebo SC Q4W and Placebo IV Q8W | Fasinumab 6 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg SC Q4W and Placebo IV Q8W |
|---|---|---|---|
| Number of subjects | 141 | 141 | 140 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 58.1 | 58.2 | 56.6 |
| standard deviation | ± 12.54 | ± 11.29 | ± 10.99 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 83 | 85 | 84 |
| Male | 58 | 56 | 56 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 7 | 4 | 4 |
| Not Hispanic or Latino | 134 | 135 | 135 |
| Not Reported | 0 | 2 | 1 |
| Race<br>Units: Subjects | | | |
| White | 127 | 119 | 118 |
| Black or African American | 13 | 19 | 19 |
| Asian | 1 | 2 | 2 |
| American Indian or Alaska Native | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Other | 0 | 0 | 1 |

| **Reporting group values** | Fasinumab 9 mg IV Q8W and Placebo SC Q4W | Total | |
|---|---|---|---|
| Number of subjects | 141 | 563 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.4 | | |
| standard deviation | ± 10.49 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 81 | 333 | |
| Male | 60 | 230 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 10 | 25 | |
| Not Hispanic or Latino | 131 | 535 | |
| Not Reported | 0 | 3 | |
| Race | | | |
| Units: Subjects | | | |
| White | 116 | 480 | |
| Black or African American | 21 | 72 | |
| Asian | 1 | 6 | |
| American Indian or Alaska Native | 1 | 2 | |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | |
| Other | 1 | 2 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo SC Q4W and Placebo IV Q8W |
| Reporting group description: | |
| Subjects randomized to the matching placebo subcutaneously (SC) every four weeks (Q4W) arm received SC placebo in a manner similar to the SC loading dose of the active groups (placebo loading dose) on Day 1 and then an SC injection of placebo at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo intravenously (IV) every 8 weeks (Q8W) was received on Day 1 and at Week 8. | |
| Reporting group title | Fasinumab 6 mg SC Q4W and Placebo IV Q8W |
| Reporting group description: | |
| Subjects randomized to the fasinumab 6 mg SC Q4W arm received fasinumab 12 mg SC on Day 1 (loading dose) and then 6 mg SC (planned maintenance dose) at Weeks 4, 8, and 12 for a total of 4 doses. Matching placebo was received via intravenous (IV) infusion Q8W on Day 1 and at Week 8. | |
| Reporting group title | Fasinumab 9 mg SC Q4W and Placebo IV Q8W |
| Reporting group description: | |
| Subjects randomized to the fasinumab 9 mg SC Q4W arm received 18 mg SC on day 1 (loading dose) and then 9 mg SC (planned maintenance dose) at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8. | |
| Reporting group title | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |
| Reporting group description: | |
| Subjects randomized to the fasinumab 9 mg IV Q8W arm received IV infusions of fasinumab 9 mg on Day 1 and Week 8, for a total of 2 doses. Matching placebo SC Q4W was received on day 1 and at weeks 4, 8, and 12. | |

### Primary: Change From Baseline in the Average Daily Low Back Pain Intensity (LBPI) Score on an 11-point Numerical Rating Scale (NRS) at Week 16

| | |
|---|---|
| End point title | Change From Baseline in the Average Daily Low Back Pain Intensity (LBPI) Score on an 11-point Numerical Rating Scale (NRS) at Week 16 |
| End point description: | |
| Average daily low back pain was assessed on an 11-point numeric rating scale (NRS) and was defined as the average of the non-missing daily LBPI NRS scores for the 7 days before and including nominal visit. Subjects described their average low back pain during the past 24 hours on a scale ranging from 0 (no pain) to 10 (worst possible pain), where higher scores indicate higher pain. Analysis was performed on modified intent to treat set (mITT) that included all randomized subject per Interactive voice response system (IVRS) who received at least one dose of study drug based on the treatment allocated (as randomized) including data up to 5 weeks after the last dose of study drug. Here, number of subjects analyzed=subjects with available data for specified timepoint. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline to Week 16 | |

| End point values | Placebo SC Q4W and Placebo IV Q8W | Fasinumab 6 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 48 | 55 | 56 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -1.7 (± 0.23) | -2.0 (± 0.23) | -2.5 (± 0.22) | -2.4 (± 0.22) |

## Statistical analyses

| **Statistical analysis title** | Fasinumab 6 mg SC Q4W vs Placebo |
|---|---|
| Statistical analysis description: | |
| Analyses are based on mixed-effect model repeated measures (MMRM) model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction. | |
| Comparison groups | Placebo SC Q4W and Placebo IV Q8W v Fasinumab 6 mg SC Q4W and Placebo IV Q8W |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3876 [1] |
| Method | Mixed-effect model analysis |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.88 |
| upper limit | 0.34 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.31 |

Notes:

[1] - Nominal p-value

| **Statistical analysis title** | Fasinumab 9 mg SC Q4W vs Placebo |
|---|---|
| Statistical analysis description: | |
| Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction. | |
| Comparison groups | Fasinumab 9 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W |
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.018 [2] |
| Method | Mixed-effect model analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.32 |
| upper limit | -0.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3 |

Notes:

[2] - Nominal p-value

| **Statistical analysis title** | Fasinumab 9 mg IV Q8W and placebo |
|---|---|

Statistical analysis description:

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

| | |
|---|---|
| Comparison groups | Fasinumab 9 mg IV Q8W and Placebo SC Q4W v Placebo SC Q4W and Placebo IV Q8W |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0288 [3] |
| Method | Mixed-effect model analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.26 |
| upper limit | -0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3 |

Notes:

[3] - Nominal p-value

## Secondary: Change From Baseline to Weeks 2, 4, 8, and 12 in the Average Low Back Pain Index Numeric Rating Scale Score (LBPI NRS)

| End point title | Change From Baseline to Weeks 2, 4, 8, and 12 in the Average Low Back Pain Index Numeric Rating Scale Score (LBPI NRS) |
|---|---|

End point description:

Low back pain intensity was assessed on an 11-point numeric rating scale (NRS) and was defined as the average of the non-missing daily LBPI NRS scores for the 7 days before and including nominal visit. Subjects described their average low back pain during the past 24 hours on a scale ranging from 0 (no pain) to 10 (worst possible pain), where higher scores indicate higher pain. Analysis was performed on modified intent to treat set mITT population. Here 'n' signifies number of subjects with available data for specified category.

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

End point timeframe:

Baseline to Week 2, 4, 8, and 12

| **End point values** | Placebo SC Q4W and Placebo IV Q8W | Fasinumab 6 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 140 | 139 | 139 | 140 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Change to Week 2 (n = 133, 135, 138, 136) | -0.9 (± 0.17) | -1.3 (± 0.17) | -1.6 (± 0.17) | -1.6 (± 0.16) |

| | | | | |
|---|---|---|---|---|
| Change to Week 4 (n = 132, 128, 132, 133) | -0.9 (± 0.17) | -1.5 (± 0.17) | -2.0 (± 0.17) | -1.9 (± 0.16) |
| Change to Week 8 (n = 98, 105, 103, 95) | -1.2 (± 0.19) | -1.8 (± 0.19) | -2.3 (± 0.19) | -2.2 (± 0.19) |
| Change to Week 12 (n = 69, 74, 76, 69) | -1.5 (± 0.21) | -2.0 (± 0.21) | -2.6 (± 0.21) | -2.5 (± 0.21) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 16 in Roland Morris Disability Questionnaire (RMDQ) Total Score

| | |
|---|---|
| End point title | Change From Baseline to Week 16 in Roland Morris Disability Questionnaire (RMDQ) Total Score |

End point description:

The RMDQ is a self-administered, widely used health status measure for LBP. It measures pain and function, using 24 items describing limitations to everyday life that can be caused by LBP. The score of the RMDQ is the total number of items checked – that is from a minimum of 0 (no disability) to a maximum of 24 (maximum disability), where lower scores indicative of better function. Analysis was performed on mITT population. Here, number of subjects analyzed=subjects with available data for specified timepoint.

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

End point timeframe:

Baseline to Week 16

| **End point values** | Placebo SC Q4W and Placebo IV Q8W | Fasinumab 6 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 46 | 46 | 55 | 55 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -3.8 (± 0.54) | -6.0 (± 0.54) | -5.8 (± 0.51) | -6.3 (± 0.51) |

### Statistical analyses

| **Statistical analysis title** | Fasinumab 6 mg SC Q4W vs Placebo |
|---|---|

Statistical analysis description:

Analyses are based on mixed-effect model repeated measures (MMRM) model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

| | |
|---|---|
| Comparison groups | Fasinumab 6 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W |

| | |
|---|---|
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0028 [4] |
| Method | Mixed-effect model analysis |
| Parameter estimate | LS mean difference |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.65 |
| upper limit | -0.77 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.73 |

Notes:

[4] - Nominal p-value

| **Statistical analysis title** | Fasinumab 9 mg SC Q4W vs Placebo |
|---|---|

Statistical analysis description:

Analyses are based on mixed-effect model repeated measures (MMRM) model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

| | |
|---|---|
| Comparison groups | Fasinumab 9 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0068 [5] |
| Method | Mixed-effect model analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.36 |
| upper limit | -0.54 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.72 |

Notes:

[5] - Nominal p-value

| **Statistical analysis title** | Fasinumab 9 mg IV Q8W and placebo |
|---|---|

Statistical analysis description:

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

| | |
|---|---|
| Comparison groups | Fasinumab 9 mg IV Q8W and Placebo SC Q4W v Placebo SC Q4W and Placebo IV Q8W |

| | |
|---|---|
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 [6] |
| Method | Mixed-effect model analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.88 |
| upper limit | -1.06 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.72 |

Notes:

[6] - Nominal p-value

## Secondary: Change From Baseline to Week 16 in the Patient Global Assessment (PGA) of Low Back Pain (LBP) Score

| | |
|---|---|
| End point title | Change From Baseline to Week 16 in the Patient Global Assessment (PGA) of Low Back Pain (LBP) Score |

End point description:

The PGA of LBP is a subject assessed 5 point Likert scale of LBP ranging from 0-5 where 1=very well; 2=well; 3=fair; 4=poor; and 5=very poor. Analysis was performed on mITT population. Here, number of subjects analyzed=subjects with available data for specified timepoint.

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

End point timeframe:

Baseline to Week 16

| **End point values** | Placebo SC Q4W and Placebo IV Q8W | Fasinumab 6 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 50 | 48 | 55 | 57 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.7 (± 0.10) | -0.9 (± 0.10) | -0.8 (± 0.10) | -1.0 (± 0.09) |

## Statistical analyses

| **Statistical analysis title** | Fasinumab 6 mg SC Q4W vs Placebo |
|---|---|

Statistical analysis description:

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

| | |
|---|---|
| Comparison groups | Fasinumab 6 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W |

| | |
|---|---|
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1501 [7] |
| Method | Mixed-effect model analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.14 |

Notes:

[7] - Nominal p-value

| **Statistical analysis title** | Fasinumab 9 mg SC Q4W vs Placebo |
|---|---|

Statistical analysis description:

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

| | |
|---|---|
| Comparison groups | Fasinumab 9 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2603 [8] |
| Method | Mixed-effect model analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | 0.11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.13 |

Notes:

[8] - Nominal p-value

| **Statistical analysis title** | Fasinumab 9 mg IV Q8W and placebo |
|---|---|

Statistical analysis description:

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

| | |
|---|---|
| Comparison groups | Fasinumab 9 mg IV Q8W and Placebo SC Q4W v Placebo SC Q4W and Placebo IV Q8W |

| | |
|---|---|
| Number of subjects included in analysis | 107 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0135 [9] |
| Method | Mixed-effect model analysis |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.59 |
| upper limit | -0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.13 |

Notes:

[9] - Nominal p-value

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Week 36) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment emergent that is AEs that developed/worsened and deaths that occurred during 'the treatment emergent period' (from the first dose of study drug up to the 4 weeks after the last dose of SC drug, or 8 weeks after the last dose of IV study drug, whichever is later).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo SC Q4W and Placebo IV Q8W |

Reporting group description:

Subjects randomized to the matching placebo SC Q4W arm received SC placebo in a manner similar to the SC loading dose of the active groups (placebo loading dose) on Day 1 and then an SC injection of placebo at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8.

| | |
|---|---|
| Reporting group title | Fasinumab 6 mg SC Q4W and Placebo IV Q8W |

Reporting group description:

Subjects randomized to the fasinumab 6 mg SC Q4W arm received fasinumab 12 mg SC on Day 1 (loading dose) and then 6 mg SC (planned maintenance dose) at Weeks 4, 8, and 12 for a total of 4 doses. Matching placebo was received via intravenous (IV) infusion Q8W on Day 1 and at Week 8.

| | |
|---|---|
| Reporting group title | Fasinumab 9 mg SC Q4W and Placebo IV Q8W |

Reporting group description:

Subjects randomized to the fasinumab 9 mg SC Q4W arm received 18 mg SC on day 1 (loading dose) and then 9 mg SC (planned maintenance dose) at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8.

| | |
|---|---|
| Reporting group title | Fasinumab 9 mg IV Q8W and Placebo SC Q4W |

Reporting group description:

Subjects randomized to the fasinumab 9 mg IV Q8W arm received IV infusions of fasinumab 9 mg on Day 1 and Week 8, for a total of 2 doses. Matching placebo SC Q4W was received on day 1 and at weeks 4, 8, and 12.

| Serious adverse events | Placebo SC Q4W and Placebo IV Q8W | Fasinumab 6 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg SC Q4W and Placebo IV Q8W |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 140 (2.86%) | 2 / 139 (1.44%) | 3 / 139 (2.16%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 140 (0.71%) | 0 / 139 (0.00%) | 0 / 139 (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 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 0 / 139 (0.00%) | 0 / 139 (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 |
| Tongue carcinoma stage iv | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | 0 / 139 (0.00%) | 0 / 139 (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 | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 1 / 139 (0.72%) | 0 / 139 (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 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 1 / 139 (0.72%) | 0 / 139 (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 |
| Eye injury | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | 0 / 139 (0.00%) | 0 / 139 (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 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 0 / 139 (0.00%) | 0 / 139 (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 |
| Patella fracture | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 0 / 139 (0.00%) | 0 / 139 (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 |

| | | | |
|---|---|---|---|
| Skull fracture | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 1 / 139 (0.72%) | 0 / 139 (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 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 0 / 139 (0.00%) | 0 / 139 (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 | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 1 / 139 (0.72%) | 0 / 139 (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 | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | 0 / 139 (0.00%) | 0 / 139 (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 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 0 / 139 (0.00%) | 1 / 139 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 0 / 139 (0.00%) | 0 / 139 (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 | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 0 / 139 (0.00%) | 1 / 139 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | 0 / 139 (0.00%) | 1 / 139 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Fasinumab 9 mg IV Q8W and Placebo SC Q4W | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 140 (3.57%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tongue carcinoma stage iv | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 140 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Placebo SC Q4W and Placebo IV Q8W | Fasinumab 6 mg SC Q4W and Placebo IV Q8W | Fasinumab 9 mg SC Q4W and Placebo IV Q8W |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 44 / 140 (31.43%) | 35 / 139 (25.18%) | 52 / 139 (37.41%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 9 / 140 (6.43%) | 9 / 139 (6.47%) | 9 / 139 (6.47%) |
| occurrences (all) | 11 | 9 | 19 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 4 / 140 (2.86%) | 4 / 139 (2.88%) | 7 / 139 (5.04%) |
| occurrences (all) | 4 | 4 | 7 |
| Paraesthesia | | | |
| subjects affected / exposed | 4 / 140 (2.86%) | 6 / 139 (4.32%) | 9 / 139 (6.47%) |
| occurrences (all) | 5 | 6 | 10 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 140 (1.43%) | 4 / 139 (2.88%) | 7 / 139 (5.04%) |
| occurrences (all) | 4 | 4 | 7 |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 17 / 140 (12.14%) | 15 / 139 (10.79%) | 16 / 139 (11.51%) |
| occurrences (all) | 22 | 26 | 24 |
| Back pain | | | |
| subjects affected / exposed | 7 / 140 (5.00%) | 0 / 139 (0.00%) | 4 / 139 (2.88%) |
| occurrences (all) | 7 | 0 | 4 |
| Pain in extremity | | | |
| subjects affected / exposed | 12 / 140 (8.57%) | 3 / 139 (2.16%) | 5 / 139 (3.60%) |
| occurrences (all) | 14 | 4 | 5 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 8 / 140 (5.71%) | 9 / 139 (6.47%) | 8 / 139 (5.76%) |
| occurrences (all) | 8 | 9 | 9 |

| **Non-serious adverse events** | Fasinumab 9 mg IV Q8W and Placebo SC Q4W | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 49 / 140 (35.00%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 9 / 140 (6.43%) | | |
| occurrences (all) | 9 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 3 / 140 (2.14%) | | |
| occurrences (all) | 3 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 9 / 140 (6.43%) | | |
| occurrences (all) | 9 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 140 (0.71%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 21 / 140 (15.00%) | | |
| occurrences (all) | 26 | | |

| | | | |
|---|---|---|---|
| Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | <br>5 / 140 (3.57%)<br>5<br><br><br>4 / 140 (2.86%)<br>7 | | |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | <br><br>10 / 140 (7.14%)<br>10 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 January 2016 | Following changes were made: - Clarified that the maximum dose of paracetamol/acetaminophen permitted as rescue medication for LBP is 2,600 mg (325 mg x 8) per day in North America, and 2,500 mg (500 mg x 5) per day in Europe, - added confirmed elevated screening ALT or AST > 2.5 x upper limit of normal (ULN) as an exclusion criterion, - added continued noncompliance with protocol-defined maximum paracetamol/acetaminophen use after appropriate counseling as a reason for permanent discontinuation of study drug, - changed the notification requirement for emergency unblinding to "The investigator should promptly document and explain to the sponsor any premature unblinding." - Made administrative edits. |
| 19 January 2016 | Following changes were made: - Incorporated revisions to ensure a consistent approach across the fasinumab program, for imaging requirements: added further detail on imaging requirements during the screening period, - specified that radiographs and/or MRI will or must (rather than should) be performed on any joint following report of a clinically significant worsening or exacerbation of pain in that joint, - specified that prior to the pre-randomization visit, - an MRI of the affected joint must be performed and assessed by the central reader for any screening radiographs that are inconclusive for potential joint-related findings and for any knee or hip joint that has a baseline K-L score of ≥3, and specified that, before a subject was randomized, confirmation must be received that there are no exclusionary finding on screening MRIs, - updated the study stopping rules to state that the DMC may recommend temporarily halting the study if the DMC has significant concerns regarding a meaningful imbalance in joint-related AEs, SNS dysfunction, or neurosensory disturbances, - added willingness to consider TJR if necessary as an inclusion criterion, modified exclusion criteria, - added clinically significant sensory and motor neurologic events grade >2 according to Common Terminology Criteria for Adverse Events (CTCAE) v.4 as a new reason for permanent discontinuation of study drug; - specified that sites should use CTCAE v.4 criteria throughout the study for consistency, - added new signs and symptoms indicative of carpal tunnel syndrome as a new reason for permanent discontinuation of study drug, - modified schedule of events, - study visit descriptions and study procedures, - refined and further detail text describing safety reporting, - and monitoring of adverse events of special interest (AESI), - refined and further detail the statistical plan, made minor clarifications and administrative edits. |
| 25 August 2016 | Following changes were made: - Added additional collection time points for urine to better monitor patient safety, - added creatinine and phosphorous to routine serum and urine chemistry sampling to better monitor patient safety, - updated the terminology from "destructive arthropathy" to "adjudicated arthropathy" to allow for consistency within the program and to allow for a more accurate description of the joint events in the trial, - updated the personnel who have the authorization to approve rescreening, - updated the reporting time for AESIs from 7 days to 24 hours. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|

| | | |
|---|---|---|
| 13 October 2016 | The Food and Drug Administration (FDA) placed the study on partial clinical hold following an adjudicated arthropathy (AA) event that occurred in a subject with chronic low back pain (LBP) and a history of advanced osteoarthritis (OA) (K-L = 3 in the AA joint at screening). | - |

Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| As a result of the partial clinical hold the Sponsor made a decision not to amend the protocol and consequently randomization and dosing was prematurely discontinued. |

Notes: