



Clinical trial results:

The primary objective of this study was to demonstrate the efficacy, safety, and tolerability of fulranumab subcutaneous (SC) injections as adjunctive therapy to opioid treatment compared with placebo SC injections in subjects who had signs and symptoms of osteoarthritis (OA) of the hip or knee that were not adequately controlled by their current pain therapy and who were planning a joint replacement surgery.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-001830-16 |
| Trial protocol | DE GB HU PL |
| Global end of trial date | 16 September 2016 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 09 September 2017 |
| First version publication date | 09 September 2017 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | 42160443PAI3001 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02336685 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Janssen Research & Development LLC |
| Sponsor organisation address | Archimedesweg 29, Leiden, Netherlands, 2333CM |
| Public contact | Clinical Registry group, Janssen Research & Development LLC, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry group, Janssen Research & Development LLC, ClinicalTrialsEU@its.jnj.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 | 16 September 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 September 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the efficacy, safety, and tolerability of fulranumab subcutaneous (SC) injections as adjunctive therapy to opioid treatment compared with placebo SC injections in subjects who had signs and symptoms of osteoarthritis (OA) of the hip or knee that were not adequately controlled by their current pain therapy and who were planning a joint replacement surgery.

Protection of trial subjects:

Safety was evaluated throughout the study and included monitoring of adverse event (AE), clinical laboratory testing, vital sign collection (including orthostatic testing), neurologic evaluation (abbreviated neurologic examination including an assessment of pupillary light reflex and signs consistent with carpal tunnel syndrome, Total Neuropathy Score-nurse [TNSn], Mini Mental State Examination [MMSE], autonomic nervous system dysfunction history, and carpal tunnel syndrome questionnaire), joint-related event evaluations (joint examinations and radiographs), numerical rating scale (NRS) for nonstudy joint pain, electrocardiograms (ECGs), physical examinations, and injection-site reactions. This study was conducted in accordance with the ethical principles that have their origin in the declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 07 August 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 13 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Country: Number of subjects enrolled | New Zealand: 2 |
| Country: Number of subjects enrolled | Poland: 4 |
| Country: Number of subjects enrolled | United States: 48 |
| Worldwide total number of subjects | 78 |
| EEA total number of subjects | 22 |

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) | 43 |
| From 65 to 84 years | 35 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 78 subjects were randomized: 26 in placebo group, 25 in fulranumab (FUL) 1 milligram (mg) every 4 week (Q4wk) group, and 27 in FUL 3 mg Q4wk group. The intent-to-treat (ITT) and safety analysis sets included all 78 subjects.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Double Blind Phase |
| 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 |

Arm description:

Subjects received 4 placebo subcutaneous (SC) injections (one injection every 4 week) for 16 weeks during double-blind treatment phase.

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

Dosage and administration details:

Subjects received 4 placebo SC injections (one injection every 4 week) for 16 weeks during double-blind treatment phase.

| | |
|------------------|-----------------|
| Arm title | Fulranumab 1 mg |
|------------------|-----------------|

Arm description:

Subjects received fulranumab 1 mg injection every 4 weeks for 16 weeks during double-blind treatment phase.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Fulranumab 1mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received fulranumab 1mg injection every 4 weeks for 16 weeks during double-blind treatment phase.

| | |
|------------------|-----------------|
| Arm title | Fulranumab 3 mg |
|------------------|-----------------|

Arm description:

Subjects received fulranumab 3 mg injection every 4 weeks for 16 weeks during double-blind treatment phase.

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

| | |
|--|--|
| Investigational medicinal product name | Fulranumab 3mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received fulranumab 3 mg injection every 4 weeks for 16 weeks during double-blind treatment phase.

| Number of subjects in period 1 | Placebo | Fulranumab 1 mg | Fulranumab 3 mg |
|--------------------------------|---------|-----------------|-----------------|
| Started | 26 | 25 | 27 |
| Completed | 7 | 7 | 8 |
| Not completed | 19 | 18 | 19 |
| Consent withdrawn by subject | - | 1 | 1 |
| Study terminated by sponsor | 18 | 17 | 17 |
| Protocol deviation | 1 | - | - |
| Lack of efficacy | - | - | 1 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | 24 Week Follow-up Phase |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | No |
| Arm title | Placebo |

Arm description:

Subjects who received placebo in treatment phase were followed for 24 weeks in this period.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Fulranumab 1 mg |

Arm description:

Subjects who received fulranumab 1 mg in treatment phase were followed for 24 weeks in this period.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Fulranumab 3 mg |

Arm description:

Subjects who received fulranumab 3 mg in treatment phase were followed for 24 weeks in this period.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | Placebo | Fulranumab 1 mg | Fulranumab 3 mg |
|---------------------------------------|---------|-----------------|-----------------|
| Started | 12 | 10 | 13 |
| Completed | 9 | 8 | 11 |
| Not completed | 3 | 2 | 2 |
| Consent withdrawn by subject | - | 1 | 1 |
| Study terminated by sponsor | 3 | - | 1 |
| Lost to follow-up | - | 1 | - |

Period 3

| | |
|------------------------------|---------------------------------------|
| Period 3 title | Limited Safety Follow-up Phase (LSFU) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | No |
| Arm title | Placebo |

Arm description:

Subjects who received placebo in treatment phase were followed for 24 weeks after the last injection of study drug in this follow up phase. Subjects who discontinued from the 24- week follow-up phase were also asked to enter the LSFU phase.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Fulranumab 1 mg |

Arm description:

Subjects who received fulranumab 1 mg in treatment phase were followed for 24 weeks after the last injection of study drug in this follow up phase. Subjects who discontinued from the 24- week follow-up phase were also asked to enter the LSFU phase.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Fulranumab 3 mg |

Arm description:

Subjects who received fulranumab 3 mg in treatment phase were followed for 24 weeks after the last injection of study drug in this follow up phase. Subjects who discontinued from the 24- week follow-up phase were also asked to enter the LSFU phase.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 3 | Placebo | Fulranumab 1 mg | Fulranumab 3 mg |
|---------------------------------------|---------|-----------------|-----------------|
| Started | 1 | 4 | 3 |
| Completed | 1 | 1 | 3 |
| Not completed | 0 | 3 | 0 |
| Study terminated by sponsor | - | 1 | - |
| Lost to follow-up | - | 2 | - |

Baseline characteristics

Reporting groups

| | |
|---|-----------------|
| Reporting group title | Placebo |
| Reporting group description: Subjects received 4 placebo subcutaneous (SC) injections (one injection every 4 week) for 16 weeks during double-blind treatment phase. | |
| Reporting group title | Fulranumab 1 mg |
| Reporting group description: Subjects received fulranumab 1 mg injection every 4 weeks for 16 weeks during double-blind treatment phase. | |
| Reporting group title | Fulranumab 3 mg |
| Reporting group description: Subjects received fulranumab 3 mg injection every 4 weeks for 16 weeks during double-blind treatment phase. | |

| Reporting group values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg |
|---|----------|-----------------|-----------------|
| Number of subjects | 26 | 25 | 27 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 12 | 15 | 16 |
| From 65 to 84 years | 14 | 10 | 11 |
| 85 years and over | 0 | 0 | 0 |
| Title for AgeContinuous Units: years | | | |
| median | 66 | 63 | 61 |
| full range (min-max) | 34 to 82 | 42 to 82 | 50 to 80 |
| Title for Gender Units: subjects | | | |
| Female | 18 | 18 | 15 |
| Male | 8 | 7 | 12 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 78 | | |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 43 | | |
| From 65 to 84 years | 35 | | |
| 85 years and over | 0 | | |
| Title for AgeContinuous Units: years | | | |
| median | - | | |
| full range (min-max) | - | | |

| | | | |
|------------------|----|--|--|
| Title for Gender | | | |
| Units: subjects | | | |
| Female | 51 | | |
| Male | 27 | | |

End points

End points reporting groups

| | |
|--|-----------------|
| Reporting group title | Placebo |
| Reporting group description: Subjects received 4 placebo subcutaneous (SC) injections (one injection every 4 week) for 16 weeks during double-blind treatment phase. | |
| Reporting group title | Fulranumab 1 mg |
| Reporting group description: Subjects received fulranumab 1 mg injection every 4 weeks for 16 weeks during double-blind treatment phase. | |
| Reporting group title | Fulranumab 3 mg |
| Reporting group description: Subjects received fulranumab 3 mg injection every 4 weeks for 16 weeks during double-blind treatment phase. | |
| Reporting group title | Placebo |
| Reporting group description: Subjects who received placebo in treatment phase were followed for 24 weeks in this period. | |
| Reporting group title | Fulranumab 1 mg |
| Reporting group description: Subjects who received fulranumab 1 mg in treatment phase were followed for 24 weeks in this period. | |
| Reporting group title | Fulranumab 3 mg |
| Reporting group description: Subjects who received fulranumab 3 mg in treatment phase were followed for 24 weeks in this period. | |
| Reporting group title | Placebo |
| Reporting group description: Subjects who received placebo in treatment phase were followed for 24 weeks after the last injection of study drug in this follow up phase. Subjects who discontinued from the 24- week follow-up phase were also asked to enter the LSFU phase. | |
| Reporting group title | Fulranumab 1 mg |
| Reporting group description: Subjects who received fulranumab 1 mg in treatment phase were followed for 24 weeks after the last injection of study drug in this follow up phase. Subjects who discontinued from the 24- week follow-up phase were also asked to enter the LSFU phase. | |
| Reporting group title | Fulranumab 3 mg |
| Reporting group description: Subjects who received fulranumab 3 mg in treatment phase were followed for 24 weeks after the last injection of study drug in this follow up phase. Subjects who discontinued from the 24- week follow-up phase were also asked to enter the LSFU phase. | |

Primary: Change from Baseline to DB-LOCF in Patient Global Assessment (PGA) Score

| | |
|--|---|
| End point title | Change from Baseline to DB-LOCF in Patient Global Assessment (PGA) Score ^[1] |
| End point description: The PGA is a single item that the patient completes to indicate their perception of their osteoarthritis status, on an 11-point numerical rating scale from 0 (Very Good) to 10 (Very Bad). The ITT analysis set was defined as all randomized subjects who received at least 1 dose of study drug. Here 'n' signifies number of subjects who were evaluable for this outcome measure at specific timepoint. | |

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline, Weeks 5, 9, 13, 17 and DB-LOCF | |
| Notes: | |
| [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. | |
| Justification: No statistical analyses have been specified for this primary end point. | |

| End point values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 | 25 | 27 | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=26,25,27) | 8.5 (± 0.95) | 7.8 (± 1.41) | 7.9 (± 1.22) | |
| Change at Week 5 (n=26,24,27) | -1.2 (± 1.29) | -1.6 (± 2.26) | -2.5 (± 2.69) | |
| Change at Week 9 (n=16,19,19) | -2.4 (± 1.82) | -2.1 (± 2.74) | -3 (± 1.76) | |
| Change at Week 13 (n=14,14,13) | -1.6 (± 1.74) | -2.6 (± 2.59) | -2.5 (± 2.44) | |
| Change at Week 17 (n=8,11,9) | -3.4 (± 2.07) | -2.1 (± 1.04) | -3 (± 2.29) | |
| Change at DB-LOCF (n=26,25,27) | -1.6 (± 1.86) | -2 (± 2.34) | -2.9 (± 2.36) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Double-Blind Phase, Last Observation Carried Forward (DB-LOCF) in Western Ontario and McMaster University Arthritis Index (WOMAC) Pain Subscale Score

| | |
|-----------------|---|
| End point title | Change From Baseline to Double-Blind Phase, Last Observation Carried Forward (DB-LOCF) in Western Ontario and McMaster University Arthritis Index (WOMAC) Pain Subscale Score |
|-----------------|---|

End point description:

The WOMAC 3.1 is a multi-dimensional, osteoarthritis (OA) specific self-administered questionnaire using 24 questions with a 48-hour recall that are grouped into 3 subscales (pain, stiffness, and physical function) associated with hip or knee OA. Pain, stiffness, and physical function is rated on a scale of 0-10, where 0=no pain to 10=extreme pain in the WOMAC pain subscale score. The ITT analysis set was defined as all randomized subjects who received at least 1 dose of study drug. Here 'n' signifies number of subjects who were evaluable for this outcome measure at specific timepoint.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 5, 9, 13, 17 and DB-LOCF | |

| End point values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 | 25 | 27 | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=26,25,27) | 7.88 (± 1.216) | 7.34 (± 1.064) | 7.6 (± 1.209) | |

| | | | | |
|--------------------------------|-----------------|-----------------|-----------------|--|
| Change at Week 5 (n=26,24,27) | -1.32 (± 0.982) | -1.45 (± 1.749) | -2.74 (± 2.181) | |
| Change at Week 9 (n=16,19,19) | -2.5 (± 1.697) | -1.93 (± 2.265) | -3.26 (± 1.764) | |
| Change at Week 13 (n=14,14,13) | -2.19 (± 1.803) | -1.91 (± 2.275) | -3.09 (± 2.042) | |
| Change at Week 17 (n=8,11,9) | -3.03 (± 2.499) | -2.27 (± 2.098) | -3.58 (± 2.099) | |
| Change at DB-LOCF (n=26,25,27) | -1.7 (± 1.686) | -2.1 (± 2.168) | -3.3 (± 2.164) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to DB-LOCF in Western Ontario and McMaster University Arthritis Index (WOMAC) Physical Function Subscale Score

| | |
|-----------------|---|
| End point title | Change From Baseline to DB-LOCF in Western Ontario and McMaster University Arthritis Index (WOMAC) Physical Function Subscale Score |
|-----------------|---|

End point description:

The WOMAC 3.1 is a multi-dimensional, osteoarthritis (OA) specific self-administered questionnaire using 24 questions with a 48-hour recall that are grouped into 3 subscales (pain, stiffness, and physical function) associated with hip or knee OA. Pain, stiffness, and physical function is rated on a scale of 0-10, where 0=no difficulty to 10=extreme difficulty in performing daily activities in the WOMAC physical function subscale score. The ITT analysis set was defined as all randomized subjects who received at least 1 dose of study drug. Here 'n' signifies number of subjects who were evaluable for this outcome measure at specific timepoint.

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

End point timeframe:

Baseline, Weeks 5, 9, 13, 17 and DB-LOCF

| End point values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg | |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 | 25 | 27 | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=26,25,27) | 7.6878 (± 1.20182) | 7.3553 (± 0.99892) | 7.6057 (± 1.14654) | |
| Change at Week 5 (n=26,24,27) | -1.0656 (± 1.71032) | -1.3725 (± 1.86183) | -2.7495 (± 2.27528) | |
| Change at Week 9 (n=16,19,19) | -1.9301 (± 1.96899) | -2.0341 (± 2.21823) | -3.1115 (± 1.52222) | |
| Change at Week 13 (n=14,14,13) | -2.1134 (± 2.21598) | -2.2689 (± 2.09003) | -3.1584 (± 1.94835) | |
| Change at Week 17 (n=8,11,9) | -2.8382 (± 2.58149) | -2.615 (± 2.07612) | 3.1634 (± 1.48632) | |
| DB-LOCF (n=26,25,27) | -1.3643 (± 1.85346) | -2.1694 (± 2.22666) | -3.0414 (± 1.9709) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Through Week 20 in Daily Numerical Rating Scale (NRS) Score

| | |
|-----------------|--|
| End point title | Change From Baseline Through Week 20 in Daily Numerical Rating Scale (NRS) Score |
|-----------------|--|

End point description:

The numerical rating scale (NRS) uses an 11-point scale to assess OA pain ranging from 0 to 10 with high scores representing greater symptom severity (0=no pain and 10=pain as bad as you can imagine). The ITT analysis set was defined as all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Baseline through Week 20

| End point values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg | |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 | 25 | 27 | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=26,25,27) | 7.7769 (± 1.44163) | 6.8533 (± 1.09333) | 7.4438 (± 1.28128) | |
| Change at Week 1-4 (n=26,25,27) | -1.1533 (± 1.36821) | -1.2905 (± 1.85651) | -2.1978 (± 2.17489) | |
| Change at Week 5-8 (n=23,24,25) | -1.7975 (± 1.73601) | -1.8026 (± 2.08613) | -2.8119 (± 2.0814) | |
| Change at Week 9-12 (n=17,21,19) | -2.0027 (± 1.91794) | -1.5794 (± 1.92197) | -2.9483 (± 2.69287) | |
| Change at Week 13-16 (n=12,15,13) | -2.9084 (± 2.37417) | -1.281 (± 1.75338) | -3.0143 (± 2.79967) | |
| Change at Week 17-20 (n=5,8,6) | -3.2362 (± 2.5395) | -2.4691 (± 1.95121) | -2.3238 (± 1.78483) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to DB-LOCF in WOMAC Stiffness Subscale Score

| | |
|-----------------|---|
| End point title | Change From Baseline to DB-LOCF in WOMAC Stiffness Subscale Score |
|-----------------|---|

End point description:

The WOMAC 3.1 is a multi-dimensional, osteoarthritis (OA) specific self-administered questionnaire using 24 questions with a 48-hour recall that are grouped into 3 subscales (pain, stiffness, and physical function) associated with hip or knee OA. Pain, stiffness, and physical function is rated on a scale of 0-10, where 0=no stiffness to 10=extreme stiffness in the WOMAC stiffness subscale score. The intent-to-treat (ITT) analysis set was defined as all randomized subjects who received at least 1 dose of study drug. Here 'n' signifies number of subjects who were evaluable for this outcome measure at specific timepoint.

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

End point timeframe:

Baseline, Weeks 5, 9, 13, 17 and DB-LOCF

| End point values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 | 25 | 27 | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=26,25,27) | 7.92 (± 1.332) | 7.34 (± 1.179) | 7.8 (± 1.325) | |
| Change at Week 5 (n=26,24,27) | -1.1 (± 1.613) | -1.69 (± 2.413) | -3.07 (± 2.623) | |
| Change at Week 9 (n=16,19,19) | -2.34 (± 2.119) | -1.84 (± 2.135) | -3 (± 1.667) | |
| Change at Week 13 (14,14,13) | -2.54 (± 2.249) | -2.39 (± 2.305) | -3.65 (± 2.258) | |
| Change at Week 17 (n=8,11,9) | -3.31 (± 2.777) | -2.27 (± 1.967) | -3.89 (± 1.764) | |
| Change at DB-LOCF (n=26,25,27) | -1.56 (± 2.146) | -1.98 (± 2.138) | -3.31 (± 2.267) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Through Double-blind Phase for Rescue Medication and Other Osteoarthritis (OA) Analgesia

| | |
|-----------------|---|
| End point title | Change From Baseline Through Double-blind Phase for Rescue Medication and Other Osteoarthritis (OA) Analgesia |
|-----------------|---|

End point description:

Use of rescue medication (acetaminophen/paracetamol) and other OA pain medication was recorded weekly during the study. The ITT analysis set was defined as all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Baseline through double-blind Phase

| End point values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg | |
|--------------------------------------|------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

[2] - Subjects were neither analyzed nor listed in the Clinical Study Report (CSR) for this end point.

[3] - Subjects were neither analyzed nor listed in the CSR for this end point.

[4] - Subjects were neither analyzed nor listed in the CSR for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Through Double-blind Phase in Medical Outcomes Study (MOS) Sleep Subscale Scores

| | |
|-----------------|---|
| End point title | Change from Baseline Through Double-blind Phase in Medical Outcomes Study (MOS) Sleep Subscale Scores |
|-----------------|---|

End point description:

The MOS Sleep Scale (acute version) contains 12 items that address aspects of sleep. Six subscale scores may be calculated including: daytime somnolence, sleep disturbances, snoring, shortness of breath or headache upon awaking, adequacy of sleep and amount of sleep plus a summary index of sleep disturbances. A higher score indicates worse sleep in most domains, but the amount of sleep and adequacy of sleep are scored in the opposite direction. The primary subscale of interest in this study is daytime somnolence. The ITT analysis set was defined as all randomized subjects who received at least 1 dose of study drug.

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

End point timeframe:

Baseline through double-Blind Phase

| End point values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg | |
|--------------------------------------|------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | 0 ^[7] | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

[5] - Subjects were neither analyzed nor listed in the CSR for this end point.

[6] - Subjects were neither analyzed nor listed in the CSR for this end point.

[7] - Subjects were neither analyzed nor listed in the CSR for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Through Double Blind Phase in Short-Form-36 Health Survey (SF-36) Subscale Score

| | |
|-----------------|---|
| End point title | Change From Baseline Through Double Blind Phase in Short-Form-36 Health Survey (SF-36) Subscale Score |
|-----------------|---|

End point description:

The Short Form-36 (SF-36) is a self-administered, generic, 36-item questionnaire designed to evaluate 8 domains of functional health and well being: physical and social functioning, physical and emotional role (role-physical, role-emotional) limitations, bodily pain, general health, vitality, mental health. The score for a section is an average of the individual question scores, which are scaled 0-100 (100=highest level of functioning). The ITT analysis set was defined as all randomized subjects who received at least 1 dose of study drug.

| | |
|-------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline through double-blind Phase | |

| End point values | Placebo | Fulranumab 1 mg | Fulranumab 3 mg | |
|--------------------------------------|------------------|------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | 0 ^[10] | |
| Units: Units on Scale | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

[8] - Subjects were neither analyzed nor listed in the CSR for this end point.

[9] - Subjects were neither analyzed nor listed in the CSR for this end point.

[10] - Subjects were neither analyzed nor listed in the CSR for this end point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 67 weeks

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | FUL 1mg |
|-----------------------|---------|

Reporting group description:

Subjects received fulranumab 1 mg injection every 4 weeks for 16 weeks during double-blind treatment phase and were followed up for 24 weeks in follow up phase (Period 2). Subjects who received Fulranumab 1mg and discontinued from the double-blind phase and did not enter the post-treatment follow-up phase were followed up for 24 weeks in LSFU phase (Period 3). Subjects who discontinued from the post-treatment follow-up phase were also followed up for 24 weeks in LSFU (Period 3).

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received 4 placebo subcutaneous (SC) injection (one injection every 4 week) for 16 weeks during double blind treatment phase (Period 1) and were followed up for 24 weeks in follow up phase (Period 2). Subjects who received placebo and discontinued from the double-blind phase and did not enter the post-treatment follow-up phase were followed up for 24 weeks in LSFU phase (Period 3). Subjects who discontinued from the post-treatment follow-up phase were also followed up for 24 weeks in LSFU (Period 3).

| | |
|-----------------------|---------|
| Reporting group title | FUL 3mg |
|-----------------------|---------|

Reporting group description:

Subjects received fulranumab 1 mg injection every 4 weeks for 16 weeks during double-blind treatment phase and were followed up for 24 weeks in follow up phase (Period 2). Subjects who received Fulranumab 3 mg and discontinued from the double-blind phase and did not enter the post-treatment follow-up phase were followed up for 24 weeks in LSFU phase (Period 3). Subjects who discontinued from the post-treatment follow-up phase were also followed up for 24 weeks in LSFU (Period 3).

| Serious adverse events | FUL 1mg | Placebo | FUL 3mg |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 26 (3.85%) | 0 / 27 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 26 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Skin Bacterial Infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 26 (3.85%) | 0 / 27 (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 |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | FUL 1mg | Placebo | FUL 3mg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 25 (72.00%) | 15 / 26 (57.69%) | 19 / 27 (70.37%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 26 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 26 (3.85%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 26 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 26 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 26 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Benign Prostatic Hyperplasia | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 26 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 26 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |

| | | | |
|---|----------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 27 (3.70%) 1 |
| Productive Cough subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 1 / 27 (3.70%) 1 |
| Sleep Disorder subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Investigations Blood Pressure Diastolic Decreased subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 6 | 4 / 26 (15.38%) 5 | 4 / 27 (14.81%) 6 |
| Heart Rate Decreased subjects affected / exposed occurrences (all) | 6 / 25 (24.00%) 6 | 6 / 26 (23.08%) 7 | 10 / 27 (37.04%) 16 |
| Blood Pressure Systolic Decreased subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | 4 / 26 (15.38%) 4 | 2 / 27 (7.41%) 2 |
| Hepatic Enzyme Increased subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Injury, poisoning and procedural complications Ligament Sprain subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Fall subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Meniscus Injury | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Procedural Pain subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 2 | 0 / 27 (0.00%) 0 |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness Exertional subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Dizziness Postural subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 3 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 26 (3.85%) 2 | 0 / 27 (0.00%) 0 |
| Hyporeflexia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 2 / 26 (7.69%) 5 | 0 / 27 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 3 / 27 (11.11%) 5 |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Nausea | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 4 / 27 (14.81%) 5 |
| Constipation subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Toothache subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Dermal Cyst subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Eczema subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Erythema subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Hypertonic Bladder subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Arthralgia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 26 (3.85%) | 1 / 27 (3.70%) |
| occurrences (all) | 2 | 1 | 2 |
| Back Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 26 (3.85%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 1 | 1 |
| Bone Cyst | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 26 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 26 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 0 | 2 |
| Joint Effusion | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 26 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Joint Swelling | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 26 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 2 | 0 | 1 |
| Joint Stiffness | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 26 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscle Spasms | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 26 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 2 | 0 | 2 |
| Musculoskeletal Chest Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 26 (3.85%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 26 (3.85%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 26 (3.85%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Neck Pain | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 26 (3.85%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---------------------|---------------------|
| Pain in Extremity subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 2 / 27 (7.41%) 2 |
| Osteoarthritis subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | 2 / 26 (7.69%) 2 | 0 / 27 (0.00%) 0 |
| Rapidly Progressive Osteoarthritis | Additional description: After review by the blinded Adjudication Committee both cases of rapidly progressive Osteoarthritis (OA) were determined to be normal OA. | | |
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 27 (7.41%) 1 |
| Synovial Cyst subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Epididymitis subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 2 |
| Lower Respiratory Tract Infection subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Oral Herpes subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Pneumonia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| Sinusitis | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Tinea Pedis subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 27 (0.00%) 0 |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Gout subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 26 (0.00%) 0 | 1 / 27 (3.70%) 2 |
| Vitamin D Deficiency subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Decreased Appetite subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 26 (0.00%) 0 | 0 / 27 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 17 February 2015 | Amendment INT-1 included the following changes: Addition of criteria to be used to alert the Independent Data Monitoring Committee (IDMC) to review events of interest (neurologic) and reference to criteria to be used by the IDMC for decisions related to the further conduct of the study based on prespecified safety based criteria (for joint replacement, neurologic, sympathetic, hepatic and renal events of interest, that is stopping criteria). |
| 18 February 2015 | Amendment INT-2 included the following changes: Addition of criteria to be used to alert the IDMC to review events of interest (neurologic) and reference to criteria to be used by the IDMC for decisions related to the further conduct of the study based on prespecified safety based criteria (for joint replacement, neurologic, sympathetic, hepatic and renal events of interest, ie, stopping criteria); clarification to improve performance of assessments and conduct of study and minor errors were noted. |
| 16 July 2015 | Amendment INT-3 included the following changes: Changes requested by ethics committees and health authorities to clarify study conduct and/or subject safety; and changes to clarify study conduct. |
| 14 December 2015 | Amendment INT-4 included the following changes: Respond to regulatory authority request to prohibit resumption of dosing for subjects who develop joint events of interest; respond to regulatory authority requests to include an assessment for carpal tunnel syndrome (CTS), at each clinic visit during the treatment periods, and at dedicated clinic visits during the safety follow-up period; clarification of what is acceptable as opioid failure in U.S. and Canada as per FDA request. clarification that a medication that is contraindicated will qualify as a failure due to intolerability; and clarify that fasting serum and urine samples are preferred for biomarker analysis; and minor errors were noted. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to discontinuation of fulranumab program by sponsor for strategic reasons, the study was closed to enrollment before being fully enrolled. Hence, the study results are limited to descriptive summaries of all safety data and select efficacy data.

Notes: