



## Clinical trial results:

### Randomized, 16-Week, Multi-Phase, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fulranumab as Monotherapy in Subjects with Signs and Symptoms of Osteoarthritis of the Hip or Knee

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2014-003879-37    |
| Trial protocol           | GB ES             |
| Global end of trial date | 15 September 2016 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 14 October 2017 |
| First version publication date | 14 October 2017 |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | 42160443PAI3002 |
|-----------------------|-----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02336698 |
| 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                       | 15 September 2016 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 15 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 (as measured by the changes from baseline to the end of Week 16 in the Western Ontario and McMaster University Osteoarthritis Index [WOMAC] pain and physical function subscale scores), safety, and tolerability of fulranumab subcutaneous (SC) injections as monotherapy 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                          | 16 July 2015 |
| Long term follow-up planned                               | Yes          |
| Long term follow-up rationale                             | Safety       |
| Long term follow-up duration                              | 12 Months    |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 5          |
| Country: Number of subjects enrolled | United States: 12 |
| Worldwide total number of subjects   | 17                |
| EEA total number of subjects         | 5                 |

Notes:

### Subjects enrolled per age group

|  |   |
|--|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|  |    |
|--|----|
| wk                                       |    |
| 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)                     | 6  |
| From 65 to 84 years                      | 11 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 17 subjects were randomized: 5 in placebo group, 25 in fulranumab (FUL) 1 milligram (mg) every 4 weeks (Q4wk) group, and 5 in FUL 3 mg Q4wk group. The intent-to-treat (ITT) and safety analysis sets included all 17 subjects.

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

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

|  |  |
|--|--|
| Arm type                               | Placebo                                      |
| 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 weeks) for 16 weeks during the double-blind treatment phase.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Fulranumab 1 mg |
|------------------|-----------------|

Arm description:

Subjects received 4 SC injections (one injection every 4 weeks) of fulranumab 1 mg during the double-blind treatment phase.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Fulranumab 1 mg                              |
| 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 1 mg injection every 4 weeks for 16 weeks during the double-blind treatment phase.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Fulranumab 3 mg |
|------------------|-----------------|

Arm description:

Subjects received 4 SC injections (one injection every 4 weeks) of fulranumab 3 mg during the double-blind treatment phase.

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

|  |  |
|--|--|
| Investigational medicinal product name | Fulranumab 3 mg                              |
| 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 the double-blind treatment phase.

| Number of subjects in period 1                   | Placebo | Fulranumab 1 mg | Fulranumab 3 mg |
|--|---------|-----------------|-----------------|
| Started  | 5       | 7               | 5               |
| Completed  | 0       | 0               | 1               |
| Not completed                                    | 5       | 7               | 4               |
| Consent withdrawn by subject                     | -       | 1               | 1               |
| Withdrawn by sponsor due to positive thc results | -       | 1               | -               |
| Study terminated by sponsor                      | 5       | 5               | 3               |

## 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      |
| <b>Arm title</b>             | 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 |                 |
| <b>Arm title</b>  | 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 |                 |
| <b>Arm title</b>  | 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 |                 |

| <b>Number of subjects in period 2</b> | Placebo | Fulranumab 1 mg | Fulranumab 3 mg |
|---------------------------------------|---------|-----------------|-----------------|
| Started                               | 4       | 2               | 5               |
| Completed                             | 2       | 2               | 1               |
| Not completed                         | 2       | 0               | 4               |
| Consent withdrawn by subject          | -       | -               | 1               |
| Study terminated by sponsor           | 2       | -               | 3               |

### Period 3

|                              |                                 |
|------------------------------|---------------------------------|
| Period 3 title               | Limited Safety Follow-up (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      |
| <b>Arm title</b>             | Placebo |

#### Arm description:

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

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

#### Arm description:

Subjects who received fulranumab 1 mg in treatment phase were followed for up to 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 asked to enter the LSFU phase.

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

#### Arm description:

Subjects who received fulranumab 3 mg in treatment phase were followed for up to 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 asked to enter the LSFU phase.

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

| <b>Number of subjects in period 3</b> | Placebo | Fulranumab 1 mg | Fulranumab 3 mg |
|---------------------------------------|---------|-----------------|-----------------|
| Started                               | 1       | 2               | 2               |
| Completed                             | 1       | 1               | 2               |
| Not completed                         | 0       | 1               | 0               |
| Study terminated by sponsor           | -       | 1               | -               |

## Baseline characteristics

### Reporting groups

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

| Reporting group values                      | Placebo  | Fulranumab 1 mg | Fulranumab 3 mg |
|---|----------|-----------------|-----------------|
| Number of subjects                          | 5        | 7               | 5               |
| Title for AgeCategorical<br>Units: subjects |          |                 |                 |
| Children (2-11 years)                       | 0        | 0               | 0               |
| Adolescents (12-17 years)                   | 0        | 0               | 0               |
| Adults (18-64 years)                        | 2        | 2               | 2               |
| From 65 to 84 years                         | 3        | 5               | 3               |
| 85 years and over                           | 0        | 0               | 0               |
| Title for AgeContinuous<br>Units: years     |          |                 |                 |
| median                                      | 70       | 70              | 65              |
| full range (min-max)                        | 62 to 78 | 57 to 79        | 58 to 72        |
| Title for Gender<br>Units: subjects         |          |                 |                 |
| Female                                      | 3        | 6               | 4               |
| Male  | 2        | 1               | 1               |

| Reporting group values                      | Total |  |  |
|---|-------|--|--|
| Number of subjects                          | 17    |  |  |
| Title for AgeCategorical<br>Units: subjects |       |  |  |
| Children (2-11 years)                       | 0     |  |  |
| Adolescents (12-17 years)                   | 0     |  |  |
| Adults (18-64 years)                        | 6     |  |  |
| From 65 to 84 years                         | 11    |  |  |
| 85 years and over                           | 0     |  |  |
| Title for AgeContinuous<br>Units: years     |       |  |  |
| median                                      |       |  |  |
| full range (min-max)                        | -     |  |  |



|                  |    |  |  |
|------------------|----|--|--|
| Title for Gender |    |  |  |
| Units: subjects  |    |  |  |
| Female           | 13 |  |  |
| Male             | 4  |  |  |

## End points

### End points reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | Placebo         |
| Reporting group description:<br>Subjects received 4 placebo subcutaneous (SC) injections (one injection every 4 weeks) for 16 weeks during the double-blind treatment phase.   |                 |
| Reporting group title  | Fulranumab 1 mg |
| Reporting group description:<br>Subjects received 4 SC injections (one injection every 4 weeks) of fulranumab 1 mg during the double-blind treatment phase.  |                 |
| Reporting group title  | Fulranumab 3 mg |
| Reporting group description:<br>Subjects received 4 SC injections (one injection every 4 weeks) of fulranumab 3 mg during the double-blind treatment phase.  |                 |
| Reporting group title  | Placebo         |
| Reporting group description:<br>Subjects who received placebo in treatment phase were followed for 24 weeks in this period.  |                 |
| Reporting group title  | Fulranumab 1 mg |
| Reporting group description:<br>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:<br>Subjects who received fulranumab 3 mg in treatment phase were followed for 24 weeks in this period.  |                 |
| Reporting group title  | Placebo         |
| Reporting group description:<br>Subjects who received placebo in treatment phase were followed for up to 24 weeks after the last injection of study drug in the limited safety follow-up phase. Subjects who discontinued from the 24-week follow-up phase were asked to enter the LSFU phase. |                 |
| Reporting group title  | Fulranumab 1 mg |
| Reporting group description:<br>Subjects who received fulranumab 1 mg in treatment phase were followed for up to 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 asked to enter the LSFU phase.       |                 |
| Reporting group title  | Fulranumab 3 mg |
| Reporting group description:<br>Subjects who received fulranumab 3 mg in treatment phase were followed for up to 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 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 <sup>[1]</sup> |
| End point description:<br>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 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. Here "99999" signifies that no subject was evaluable at specified time points Week 13 and 17 (Placebo group); Standard Deviation could not be calculated as only 1 subject was evaluable at specific time points Week 13 and 17 (Fulranumab 1 mg and 3 mg groups). |   |
| 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: Only descriptive statistical analysis was performed for this outcome measure due to the small number of subjects subsequent to premature closure of the study.

| End point values                     | Placebo         | Fulranumab 1 mg | Fulranumab 3 mg |  |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed          | 5               | 7               | 5               |  |
| Units: units on Scale                |                 |                 |                 |  |
| arithmetic mean (standard deviation) |                 |                 |                 |  |
| Baseline (n=5,7,5)                   | 7.8 (± 0.84)    | 8.1 (± 1.35)    | 8 (± 1.58)      |  |
| Change at Week 5 (n=4,4,3)           | -1.3 (± 0.5)    | -2 (± 1.41)     | -3.3 (± 2.52)   |  |
| Change at Week 9 (n=2,2,2)           | -1 (± 0)        | -3.5 (± 0.71)   | -4.5 (± 0.71)   |  |
| Change at Week 13 (n=0,1,1)          | 99999 (± 99999) | -2 (± 99999)    | -7 (± 99999)    |  |
| Change at Week 17 (n=0,1,1)          | 99999 (± 99999) | -2 (± 99999)    | -7 (± 99999)    |  |
| Change at DB-LOCF (n=4,4,3)          | -1.3 (± 0.5)    | -2.3 (± 1.71)   | -4.7 (± 2.08)   |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Treatment-Emergent Adverse Events as a Measure of Safety and Tolerability

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events as a Measure of Safety and Tolerability <sup>[2]</sup> |
|-----------------|--|

End point description:

An adverse event is any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product.

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

End point timeframe:

Baseline Up to 16 Weeks

Notes:

[2] - 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: Only descriptive statistical analysis was performed for this outcome measure due to the small number of subjects subsequent to premature closure of the study.

| End point values            | Placebo         | Fulranumab 1 mg | Fulranumab 3 mg |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 5               | 7               | 5               |  |
| Units: subjects             | 2               | 1               | 2               |  |

## 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 are rated on a scale of 0-10, where 0=no pain to 10=extreme pain in the WOMAC pain 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. Here "99999" signifies that no subject was evaluable at specified time points Week 13 and 17 (Placebo group); Standard Deviation (SD) could not be calculated as only 1 subject was evaluable at specific time points Week 13 and 17 (Fulranumab 1 mg and 3 mg groups).

|                |           |
|----------------|-----------|
| 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          | 5               | 7               | 5               |  |
| Units: units on Scale                |                 |                 |                 |  |
| arithmetic mean (standard deviation) |                 |                 |                 |  |
| Baseline (n=5,7,5)                   | 7.24 (± 0.921)  | 8.03 (± 1.023)  | 8 (± 1.356)     |  |
| Change at Week 5 (n=4,4,3)           | -1.35 (± 1.399) | -2.6 (± 1.575)  | -3.53 (± 1.137) |  |
| Change at Week 9 (n=2,2,2)           | -0.9 (± 1.556)  | -2.1 (± 0.424)  | -3.1 (± 1.556)  |  |
| Change at Week 13 (n=0,1,1)          | 99999 (± 99999) | -0.2 (± 99999)  | -6.8 (± 99999)  |  |
| Change at Week 17 (n=0,1,1)          | 99999 (± 99999) | -2.4 (± 99999)  | -6.8 (± 99999)  |  |
| Change at DB-LOCF (n=4,4,3)          | -1.55 (± 1.427) | -2.7 (± 1.428)  | -3.8 (± 2.615)  |  |

## 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) Physical Function 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) 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. Here "99999" signifies that no subject was evaluable at specified time points Week 13 and 17 (Placebo group); Standard Deviation (SD) could not be calculated as only 1 subject was evaluable at specific time points Week 13 and 17 (Fulranumab 1 mg and 3 mg groups).

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

**End point timeframe:**

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

| <b>End point values</b>              | Placebo             | Fulranumab 1 mg     | Fulranumab 3 mg     |  |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed          | 5                   | 7                   | 5                   |  |
| Units: units on Scale                |                     |                     |                     |  |
| arithmetic mean (standard deviation) |                     |                     |                     |  |
| Baseline (n=5,7,5)                   | 7.0588 (± 0.72879)  | 7.6471 (± 1.35932)  | 7.8235 (± 1.47646)  |  |
| Change at Week 5 (n=4,4,3)           | -0.75 (± 0.49536)   | -1.6618 (± 1.5896)  | -3.4706 (± 1.5328)  |  |
| Change at Week 9 (n=2,2,2)           | -0.8824 (± 0.33276) | -3.2353 (± 1.58059) | -5.0882 (± 0.12478) |  |
| Change at Week 13 (n=0,1,1)          | 99999 (± 99999)     | -0.7059 (± 99999)   | -6.5882 (± 99999)   |  |
| Change at Week 17 (n=0,1,1)          | 99999 (± 99999)     | -2.2353 (± 99999)   | -6.5882 (± 99999)   |  |
| Change at DB-LOCF (n=4,4,3)          | -0.9412 (± 0.43492) | -2.4853 (± 1.90451) | -4.6863 (± 2.07667) |  |

**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. Here 'n' signifies number of subjects who were evaluable for this outcome measure at specific timepoint. Here "99999" signifies that no subject was evaluable at specified time points Week 13-16 and 17-20 (Placebo group); Standard Deviation (SD) could not be calculated as only 1 subject was evaluable at specified time points Week 9-12 (Placebo and Fulranumab 1 mg groups), Week 13-16 and 17-20 (Fulranumab 1 mg and 3 mg groups).

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

**End point timeframe:**

Baseline, Weeks 1-4, 5-8, 9-12, 13-16 and 17-20

| End point values                     | Placebo             | Fulranumab 1 mg     | Fulranumab 3 mg     |  |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed          | 5                   | 7                   | 5                   |  |
| Units: units on Scale                |                     |                     |                     |  |
| arithmetic mean (standard deviation) |                     |                     |                     |  |
| Baseline (n=5,7,5)                   | 7.4667 (± 1.30384)  | 7.5524 (± 1.35508)  | 8.09 (± 1.01514)    |  |
| Change at Week 1-4 (n=5,7,5)         | -0.7524 (± 1.02362) | -0.7565 (± 1.02343) | -2.3186 (± 1.938)   |  |
| Change at Week 5-8 (n=3,3,3)         | -2.2619 (± 1.55566) | -1.0714 (± 0.70991) | -2.4562 (± 0.79051) |  |
| Change at Week 9-12 (n=1,1,2)        | -4 (± 99999)        | -1.119 (± 99999)    | -4.2143 (± 3.83858) |  |
| Change at Week 13-16 (n=0,1,1)       | 99999 (± 99999)     | -1.3333 (± 99999)   | -7.5 (± 99999)      |  |
| Change at Week 17-20 (n=0,1,1)       | 99999 (± 99999)     | -1.3333 (± 99999)   | -7.5 (± 99999)      |  |

## 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:   |   |
| <p>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 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. Here "99999" indicates that no subject was evaluable at Week 13 and Week 17 for placebo group. Here "99999" indicates that Standard deviation (SD) was not calculated for Fulranumab 1 mg and 3 mg groups as there was only 1 subject who was evaluable in the arms at a given timepoint.</p> |   |
| 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          | 5               | 7               | 5               |  |
| Units: units on Scale                |                 |                 |                 |  |
| arithmetic mean (standard deviation) |                 |                 |                 |  |
| Baseline (n=5,7,5)                   | 6.6 (± 1.084)   | 7.5 (± 1.354)   | 7.7 (± 1.718)   |  |
| Change at Week 5 (n=4,4,3)           | -0.63 (± 1.315) | -1.5 (± 1.472)  | -3.33 (± 1.528) |  |
| Change at Week 9 (n=2,2,2)           | -1 (± 0)        | -2 (± 0.707)    | -4.5 (± 3.536)  |  |
| Change at Week 13 (0,1,1)            | 99999 (± 99999) | -2 (± 99999)    | -7 (± 99999)    |  |
| Change at Week 17 (n=0,1,1)          | 99999 (± 99999) | -4 (± 99999)    | -7 (± 99999)    |  |
| Change at DB-LOCF (n=4,4,3)          | -1.13 (± 1.031) | -2 (± 1.958)    | -4 (± 2.646)    |  |

### 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.

|                |           |
|----------------|-----------|
| 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 <sup>[3]</sup> | 0 <sup>[4]</sup> | 0 <sup>[5]</sup> |  |
| Units: units on Scale                |                  |                  |                  |  |
| arithmetic mean (standard deviation) | ()               | ()               | ()               |  |

Notes:

[3] - Analysis of this endpoint was not done because the program was terminated.

[4] - Analysis of this endpoint was not done because the program was terminated.

[5] - Analysis of this endpoint was not done because the program was terminated.

### Statistical analyses

No statistical analyses for this end point

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

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|                 |   |
|-----------------|---|
| 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).

|                |           |
|----------------|-----------|
| 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 <sup>[6]</sup> | 0 <sup>[7]</sup> | 0 <sup>[8]</sup> |  |
| Units: units on Scale                |                  |                  |                  |  |
| arithmetic mean (standard deviation) | ()               | ()               | ()               |  |

Notes:

[6] - Analysis of this endpoint was not done because the program was terminated.

[7] - Analysis of this endpoint was not done because the program was terminated.

[8] - Analysis of this endpoint was not done because the program was terminated.

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of Subjects With Additional Analgesics Medication Use Through Double-blind Phase**

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|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Additional Analgesics Medication Use Through Double-blind Phase |
|-----------------|---|

End point description:

Use 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:

Up to 67 weeks

---

| End point values            | Placebo          | Fulranumab 1 mg   | Fulranumab 3 mg   |  |
|-----------------------------|------------------|-------------------|-------------------|--|
| Subject group type          | Reporting group  | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 0 <sup>[9]</sup> | 0 <sup>[10]</sup> | 0 <sup>[11]</sup> |  |
| Units: Subjects             |                  |                   |                   |  |

Notes:

[9] - Analysis of this endpoint was not done because the program was terminated.

[10] - Analysis of this endpoint was not done because the program was terminated.



[11] - Analysis of this endpoint was not done because the program was terminated.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects who Developed Antibodies to Fulranumab

|                 |   |
|-----------------|---|
| End point title | Number of Subjects who Developed Antibodies to Fulranumab |
|-----------------|---|

End point description:

Number of subjects who developed antibodies to fulranumab were assessed.

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

End point timeframe:

Baseline Up to 67 weeks

| End point values            | Placebo         | Fulranumab 1 mg | Fulranumab 3 mg |  |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed | 5               | 7               | 5               |  |
| Units: subjects             | 0               | 0               | 0               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentrations for Fulranumab

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Plasma Concentrations for Fulranumab |
|-----------------|--------------------------------------|

End point description:

Plasma Concentrations for Fulranumab were assessed.

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

End point timeframe:

Up to 67 weeks

| End point values                     | Placebo           | Fulranumab 1 mg   | Fulranumab 3 mg   |  |
|--------------------------------------|-------------------|-------------------|-------------------|--|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed          | 0 <sup>[12]</sup> | 0 <sup>[13]</sup> | 0 <sup>[14]</sup> |  |
| Units: nanogram/milliliter (ng/mL)   |                   |                   |                   |  |
| arithmetic mean (standard deviation) | ()                | ()                | ()                |  |

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Notes:

[12] - Due to less number of subjects treated, only few samples were collected. No PK analyses was done.

[13] - Due to less number of subjects treated, only few samples were collected. No PK analyses was done.

[14] - Due to less number of subjects treated, only few samples were collected. No PK analyses was done.

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### **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 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| 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 up to 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 | Fulranumab 1 mg |
|-----------------------|-----------------|

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 1 mg and discontinued from the double-blind phase and did not enter the post-treatment follow-up phase were followed-up for up to 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 | Fulranumab 3 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects received fulranumab 3 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 up to 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                            | Placebo       | Fulranumab 1 mg | Fulranumab 3 mg |
|---|---------------|-----------------|-----------------|
| Total subjects affected by serious adverse events |               |                 |                 |
| subjects affected / exposed                       | 0 / 5 (0.00%) | 0 / 7 (0.00%)   | 0 / 5 (0.00%)   |
| number of deaths (all causes)                     | 0             | 0               | 0               |
| number of deaths resulting from adverse events    |               |                 |                 |

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

| <b>Non-serious adverse events</b>                     | Placebo        | Fulranumab 1 mg | Fulranumab 3 mg |
|---|----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events |                |                 |                 |
| subjects affected / exposed                           | 2 / 5 (40.00%) | 2 / 7 (28.57%)  | 2 / 5 (40.00%)  |
| Investigations  |                |                 |                 |
| Blood Pressure Diastolic Decreased                    |                |                 |                 |
| subjects affected / exposed                           | 1 / 5 (20.00%) | 1 / 7 (14.29%)  | 2 / 5 (40.00%)  |
| occurrences (all)                                     | 1              | 1               | 2               |
| Blood Pressure Systolic Decreased                     |                |                 |                 |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 1 / 7 (14.29%)  | 2 / 5 (40.00%)  |
| occurrences (all)                                     | 0              | 1               | 2               |
| Gamma-Glutamyltransferase Increased                   |                |                 |                 |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 1 / 7 (14.29%)  | 0 / 5 (0.00%)   |
| occurrences (all)                                     | 0              | 1               | 0               |
| Heart Rate Decreased                                  |                |                 |                 |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 1 / 7 (14.29%)  | 0 / 5 (0.00%)   |
| occurrences (all)                                     | 0              | 1               | 0               |
| Nervous system disorders                              |                |                 |                 |
| Carpal Tunnel Syndrome                                |                |                 |                 |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 1 / 7 (14.29%)  | 0 / 5 (0.00%)   |
| occurrences (all)                                     | 0              | 1               | 0               |
| General disorders and administration site conditions  |                |                 |                 |
| Fatigue   |                |                 |                 |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 1 / 7 (14.29%)  | 0 / 5 (0.00%)   |
| occurrences (all)                                     | 0              | 1               | 0               |
| Eye disorders   |                |                 |                 |
| Retinal Haemorrhage                                   |                |                 |                 |
| subjects affected / exposed                           | 1 / 5 (20.00%) | 0 / 7 (0.00%)   | 0 / 5 (0.00%)   |
| occurrences (all)                                     | 1              | 0               | 0               |
| Retinal Vein Occlusion                                |                |                 |                 |
| subjects affected / exposed                           | 1 / 5 (20.00%) | 0 / 7 (0.00%)   | 0 / 5 (0.00%)   |
| occurrences (all)                                     | 1              | 0               | 0               |
| Respiratory, thoracic and mediastinal disorders       |                |                 |                 |
| Sleep Apnoea Syndrome                                 |                |                 |                 |
| subjects affected / exposed                           | 0 / 5 (0.00%)  | 1 / 7 (14.29%)  | 0 / 5 (0.00%)   |
| occurrences (all)                                     | 0              | 1               | 0               |
| Musculoskeletal and connective tissue disorders       |                |                 |                 |

|  |                    |                     |                     |
|--|--------------------|---------------------|---------------------|
| Muscle Spasms<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 | 0 / 5 (0.00%)<br>0  |
| Infections and infestations<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)              | 0 / 5 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 | 0 / 5 (0.00%)<br>0  |
| Metabolism and nutrition disorders<br>Vitamin D Deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 |

## 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: Response to regulatory authority requests and improve the overall study design and conduct.   |
| 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.   |
| 15 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: