



## Clinical trial results:

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

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2014-003224-40          |
| Trial protocol           | DE ES CZ HU SE PL GB IT |
| Global end of trial date | 19 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 | 42160443PAI3007 |
|-----------------------|-----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02301234 |
| 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                       | 19 September 2016 |
| Is this the analysis of the primary completion data? | No                |

|                                  |                   |
|----------------------------------|-------------------|
| Global end of trial reached?     | Yes               |
| Global end of trial date         | 19 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 safety, and tolerability of fulranumab subcutaneous (SC) injections compared with placebo SC injections in subjects treated with standard of care 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 events (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                          | 26 March 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 | Australia: 2          |
| Country: Number of subjects enrolled | Canada: 8             |
| Country: Number of subjects enrolled | Spain: 13             |
| Country: Number of subjects enrolled | United Kingdom: 17    |
| Country: Number of subjects enrolled | Hungary: 2            |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Poland: 5             |
| Country: Number of subjects enrolled | Sweden: 3             |
| Country: Number of subjects enrolled | United States: 58     |
| Worldwide total number of subjects   | 109                   |
| EEA total number of subjects         | 40                    |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 57 |
| From 65 to 84 years                       | 51 |
| 85 years and over                         | 1  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 111 subjects were randomized: 37 in the placebo group, 36 in the fulranumab (FUL) 1 mg every 4 Weeks (Q4wk) group, and 38 in the FUL 3 mg Q4wk group. There were 2 subjects who were randomized but were not treated.

### Period 1

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

### 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 milligram (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 milligram (mg) | Fulranumab 3 mg |
|---|---------|-----------------------------|-----------------|
| Started   | 37      | 35                          | 37              |
| Completed   | 15      | 10                          | 19              |
| Not completed                                     | 22      | 25                          | 18              |
| Consent withdrawn by subject                      | 2       | 6                           | -               |
| Subjects medical records revealed subject has HIV | 1       | -                           | -               |
| Adverse event, non-fatal                          | -       | -                           | 1               |
| Study terminated by sponsor                       | 19      | 19                          | 17              |

## 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                               | 22      | 20              | 27              |
| Completed                             | 12      | 13              | 19              |
| Not completed                         | 10      | 7               | 8               |
| Consent withdrawn by subject          | 1       | -               | 3               |
| Physician decision                    | -       | 1               | -               |
| Adverse event                         | 1       | -               | -               |
| Study terminated by sponsor           | 8       | 6               | 5               |

### 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? | Yes     |
| <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 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 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                               | 6       | 2               | 2               |
| Completed                             | 5       | 1               | 2               |
| Not completed                         | 1       | 1               | 0               |
| Consent withdrawn by subject          | 1       | -               | -               |
| Study terminated by sponsor           | -       | 1               | -               |

## Baseline characteristics

### 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 milligram (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 values                      | Placebo  | Fulranumab 1 milligram (mg) | Fulranumab 3 mg |
|---|----------|-----------------------------|-----------------|
| Number of subjects                          | 37       | 35                          | 37              |
| Title for AgeCategorical<br>Units: subjects |          |                             |                 |
| Children (2-11 years)                       | 0        | 0                           | 0               |
| Adolescents (12-17 years)                   | 0        | 0                           | 0               |
| Adults (18-64 years)                        | 17       | 21                          | 19              |
| From 65 to 84 years                         | 20       | 13                          | 18              |
| 85 years and over                           | 0        | 1                           | 0               |
| Title for AgeContinuous<br>Units: years     |          |                             |                 |
| median                                      | 65       | 61                          | 64              |
| full range (min-max)                        | 49 to 81 | 43 to 85                    | 38 to 82        |
| Title for Gender<br>Units: subjects         |          |                             |                 |
| Female                                      | 27       | 27                          | 16              |
| Male  | 10       | 8                           | 21              |

| Reporting group values                      | Total |  |  |
|---|-------|--|--|
| Number of subjects                          | 109   |  |  |
| Title for AgeCategorical<br>Units: subjects |       |  |  |
| Children (2-11 years)                       | 0     |  |  |
| Adolescents (12-17 years)                   | 0     |  |  |
| Adults (18-64 years)                        | 57    |  |  |
| From 65 to 84 years                         | 51    |  |  |
| 85 years and over                           | 1     |  |  |
| Title for AgeContinuous<br>Units: years     |       |  |  |
| median                                      |       |  |  |
| full range (min-max)                        | -     |  |  |



|                  |    |  |  |
|------------------|----|--|--|
| Title for Gender |    |  |  |
| Units: subjects  |    |  |  |
| Female           | 70 |  |  |
| Male             | 39 |  |  |

## 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 milligram (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 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 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: 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>[1]</sup> |
| End point description:<br>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:<br>Baseline Up to 16 weeks   |  |

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 milligram (mg) | Fulranumab 3 mg |  |
|-----------------------------|-----------------|-----------------------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group             | Reporting group |  |
| Number of subjects analysed | 37              | 35                          | 37              |  |
| Units: subjects             | 20              | 23                          | 20              |  |

## 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 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 milligram (mg) | Fulranumab 3 mg |  |
|--------------------------------------|-----------------|-----------------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group             | Reporting group |  |
| Number of subjects analysed          | 37              | 35                          | 37              |  |
| Units: units on scale                |                 |                             |                 |  |
| arithmetic mean (standard deviation) |                 |                             |                 |  |
| Baseline (n=37,35,37)                | 7.49 (± 1.273)  | 7.41 (± 0.982)              | 7.36 (± 0.958)  |  |
| Change at Week 5 (n=35,33,36)        | -1.78 (± 1.67)  | -2.35 (± 2.402)             | -2.87 (± 1.93)  |  |
| Change at Week 9 (n=30,23,28)        | -2.03 (± 2.198) | -3.06 (± 2.491)             | -3.19 (± 2.257) |  |
| Change at Week 13 (n=22,18,22)       | -3.09 (± 2.181) | -3.98 (± 2.515)             | -3.87 (± 2.396) |  |
| Change at Week 17 (n=17,16,17)       | -2.95 (± 1.906) | -2.73 (± 2.399)             | -3.36 (± 2.048) |  |
| Change at DB-LOCF (n=35,34,36)       | -2.32 (± 2.46)  | -2.8 (± 2.6)                | -2.89 (± 1.973) |  |

## 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.

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

End point timeframe:

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

| End point values                     | Placebo             | Fulranumab 1 milligram (mg) | Fulranumab 3 mg     |  |
|--------------------------------------|---------------------|-----------------------------|---------------------|--|
| Subject group type                   | Reporting group     | Reporting group             | Reporting group     |  |
| Number of subjects analysed          | 37                  | 35                          | 37                  |  |
| Units: units on scale                |                     |                             |                     |  |
| arithmetic mean (standard deviation) |                     |                             |                     |  |
| Baseline (n=37,35,37)                | 7.5835 (± 1.20587)  | 7.3647 (± 0.94612)          | 7.4149 (± 0.9491)   |  |
| Change at Week 5 (n=35,33,36)        | -1.8504 (± 1.61129) | -2.3369 (± 2.48665)         | -2.8644 (± 2.15375) |  |
| Change at Week 9 (n=30,23,28)        | -2.0667 (± 2.17659) | -3.0384 (± 2.50514)         | -3.145 (± 2.24025)  |  |
| Change at Week 13 (n=22,18,22)       | -2.9759 (± 1.97585) | -3.9314 (± 2.7548)          | -3.7032 (± 2.38642) |  |
| Change at Week 17 (n=17,16,17)       | -2.7439 (± 1.92551) | -2.7721 (± 2.37119)         | -3.5087 (± 2.31597) |  |
| Change at DB-LOCF (n=35,34,36)       | -2.2336 (± 2.28552) | -2.6869 (± 2.62679)         | -2.8235 (± 2.10876) |  |

## 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 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 milligram (mg) | Fulranumab 3 mg |  |
|--------------------------------------|-----------------|-----------------------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group             | Reporting group |  |
| Number of subjects analysed          | 37              | 35                          | 37              |  |
| Units: units on scale                |                 |                             |                 |  |
| arithmetic mean (standard deviation) |                 |                             |                 |  |
| Baseline (n=37,35,37)                | 7.3 (± 1.984)   | 7.26 (± 1.268)              | 7.24 (± 1.342)  |  |
| Change at Week 5 (n=35,33,36)        | -2.04 (± 1.961) | -2.41 (± 2.112)             | -2.53 (± 2.378) |  |
| Change at Week 9 (n=30,23,28)        | -2.25 (± 2.153) | -2.93 (± 2.347)             | -2.82 (± 2.622) |  |
| Change at Week 13 (n=22,18,22)       | -3.25 (± 2.022) | -3.94 (± 2.673)             | -3.05 (± 2.815) |  |
| Change at Week 17 (n=17,16,17)       | -2.94 (± 1.886) | -2.56 (± 2.358)             | -3.24 (± 2.699) |  |
| Change at DB-LOCF (n=35,34,36)       | -2.39 (± 2.298) | -2.6 (± 2.351)              | -2.54 (± 2.328) |  |

### 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).

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

End point timeframe:

Baseline through double-blind phase

| End point values                     | Placebo          | Fulranumab 1 milligram (mg) | Fulranumab 3 mg  |  |
|--------------------------------------|------------------|-----------------------------|------------------|--|
| Subject group type                   | Reporting group  | Reporting group             | Reporting group  |  |
| Number of subjects analysed          | 0 <sup>[2]</sup> | 0 <sup>[3]</sup>            | 0 <sup>[4]</sup> |  |
| Units: units on scale                |                  |                             |                  |  |
| arithmetic mean (standard deviation) | ()               | ()                          | ()               |  |

Notes:

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

[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.

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| 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. Here 'N' signifies number of subjects analysed for this endpoint.

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

End point timeframe:

Up to 67 weeks

| End point values            | Placebo         | Fulranumab 1 milligram (mg) | Fulranumab 3 mg |  |
|-----------------------------|-----------------|-----------------------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group             | Reporting group |  |
| Number of subjects analysed | 22              | 21                          | 21              |  |
| Units: subjects             | 23              | 23                          | 23              |  |

## 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:

Up to 67 weeks

| End point values            | Placebo         | Fulranumab 1 milligram (mg) | Fulranumab 3 mg |  |
|-----------------------------|-----------------|-----------------------------|-----------------|--|
| Subject group type          | Reporting group | Reporting group             | Reporting group |  |
| Number of subjects analysed | 37              | 35                          | 37              |  |
| Units: subjects             | 0               | 1                           | 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 milligram (mg) | Fulranumab 3 mg  |  |
|--------------------------------------|------------------|-----------------------------|------------------|--|
| Subject group type                   | Reporting group  | Reporting group             | Reporting group  |  |
| Number of subjects analysed          | 0 <sup>[5]</sup> | 0 <sup>[6]</sup>            | 0 <sup>[7]</sup> |  |
| Units: nanogram/milliliter (ng/mL)   |                  |                             |                  |  |
| arithmetic mean (standard deviation) | ()               | ()                          | ()               |  |

Notes:

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

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

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

### 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 (FUL) 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 | FUL 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 (FUL) 1 mg | FUL 3 mg       |
|---|----------------|-----------------------|----------------|
| Total subjects affected by serious adverse events                   |                |                       |                |
| subjects affected / exposed   | 3 / 37 (8.11%) | 3 / 35 (8.57%)        | 1 / 37 (2.70%) |
| number of deaths (all causes)                                       | 0              | 0                     | 0              |
| number of deaths resulting from adverse events                      |                |                       |                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                       |                |
| Rectal Cancer Stage Iv  |                |                       |                |
| subjects affected / exposed   | 1 / 37 (2.70%) | 0 / 35 (0.00%)        | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0                 | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0                 | 0 / 0          |
| Vascular disorders  |                |                       |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| Deep Vein Thrombosis                            |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Spigelian Hernia                                |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (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          |
| Hepatobiliary disorders                         |                |                |                |
| Biliary Colic                                   |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (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          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Pneumothorax Spontaneous                        |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (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          |
| Pulmonary Thrombosis                            |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Osteoarthritis                                  |                |                |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Bronchitis                                      |                |                |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cellulitis                                      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (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 %

| <b>Non-serious adverse events</b>                     | Placebo          | fulranumab (FUL) 1 mg | FUL 3 mg         |
|---|------------------|-----------------------|------------------|
| Total subjects affected by non-serious adverse events |                  |                       |                  |
| subjects affected / exposed                           | 21 / 37 (56.76%) | 31 / 35 (88.57%)      | 26 / 37 (70.27%) |
| Vascular disorders                                    |                  |                       |                  |
| Hypertension  |                  |                       |                  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   | 0 / 35 (0.00%)        | 1 / 37 (2.70%)   |
| occurrences (all)                                     | 1                | 0                     | 1                |
| Hypotension   |                  |                       |                  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   | 5 / 35 (14.29%)       | 2 / 37 (5.41%)   |
| occurrences (all)                                     | 3                | 6                     | 2                |
| Orthostatic Hypotension                               |                  |                       |                  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   | 0 / 35 (0.00%)        | 2 / 37 (5.41%)   |
| occurrences (all)                                     | 1                | 0                     | 2                |
| Peripheral Coldness                                   |                  |                       |                  |
| subjects affected / exposed                           | 0 / 37 (0.00%)   | 2 / 35 (5.71%)        | 0 / 37 (0.00%)   |
| occurrences (all)                                     | 0                | 2                     | 0                |
| General disorders and administration site conditions  |                  |                       |                  |
| Fatigue   |                  |                       |                  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   | 1 / 35 (2.86%)        | 0 / 37 (0.00%)   |
| occurrences (all)                                     | 1                | 1                     | 0                |
| Feeling Hot   |                  |                       |                  |
| subjects affected / exposed                           | 0 / 37 (0.00%)   | 1 / 35 (2.86%)        | 0 / 37 (0.00%)   |
| occurrences (all)                                     | 0                | 1                     | 0                |
| Injection Site Induration                             |                  |                       |                  |
| subjects affected / exposed                           | 0 / 37 (0.00%)   | 0 / 35 (0.00%)        | 1 / 37 (2.70%)   |
| occurrences (all)                                     | 0                | 0                     | 1                |
| Oedema Peripheral                                     |                  |                       |                  |
| subjects affected / exposed                           | 1 / 37 (2.70%)   | 0 / 35 (0.00%)        | 0 / 37 (0.00%)   |
| occurrences (all)                                     | 2                | 0                     | 0                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Pain  |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 2              | 0              |
| Peripheral Swelling                             |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Vessel Puncture Site Haematoma                  |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 3              | 0              |
| Reproductive system and breast disorders        |                |                |                |
| Uterine Prolapse                                |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Asthma  |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Chronic Obstructive Pulmonary Disease           |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Cough   |                |                |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Epistaxis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Nasal Congestion                                |                |                |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Oropharyngeal Pain                              |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Pulmonary Mass                                  |                |                |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |

|   |                      |                        |                       |
|---|----------------------|------------------------|-----------------------|
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 37 (2.70%)<br>1  | 0 / 35 (0.00%)<br>0    | 0 / 37 (0.00%)<br>0   |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 37 (0.00%)<br>0  | 1 / 35 (2.86%)<br>1    | 0 / 37 (0.00%)<br>0   |
| Investigations<br>Blood Pressure Diastolic Decreased<br>subjects affected / exposed<br>occurrences (all)                  | 6 / 37 (16.22%)<br>9 | 5 / 35 (14.29%)<br>5   | 8 / 37 (21.62%)<br>12 |
| Blood Pressure Increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 37 (0.00%)<br>0  | 0 / 35 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1   |
| Blood Pressure Systolic Decreased<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 37 (10.81%)<br>7 | 4 / 35 (11.43%)<br>8   | 4 / 37 (10.81%)<br>5  |
| Electrocardiogram Abnormal<br>subjects affected / exposed<br>occurrences (all)  | 0 / 37 (0.00%)<br>0  | 1 / 35 (2.86%)<br>1    | 0 / 37 (0.00%)<br>0   |
| Haemoglobin Decreased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 37 (0.00%)<br>0  | 0 / 35 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1   |
| Heart Rate Decreased<br>subjects affected / exposed<br>occurrences (all)  | 6 / 37 (16.22%)<br>8 | 10 / 35 (28.57%)<br>12 | 6 / 37 (16.22%)<br>6  |
| Heart Rate Increased<br>subjects affected / exposed<br>occurrences (all)  | 1 / 37 (2.70%)<br>1  | 0 / 35 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1   |
| Weight Increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 37 (0.00%)<br>0  | 0 / 35 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1   |
| Injury, poisoning and procedural complications<br>Accidental Overdose<br>subjects affected / exposed<br>occurrences (all) | 0 / 37 (0.00%)<br>0  | 1 / 35 (2.86%)<br>1    | 0 / 37 (0.00%)<br>0   |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Back Injury                 |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Burns First Degree          |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Contusion                   |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Epicondylitis               |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 0              | 1              |
| Fall                        |                |                |                |
| subjects affected / exposed | 3 / 37 (8.11%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 4              | 1              | 0              |
| Foot Fracture               |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 0              | 1              |
| Injection Related Reaction  |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Joint Injury                |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 2 / 37 (5.41%) |
| occurrences (all)           | 0              | 1              | 2              |
| Laceration                  |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 0              | 1              |
| Ligament Sprain             |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Muscle Strain               |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 2 / 37 (5.41%) |
| occurrences (all)           | 0              | 1              | 2              |
| Nail Avulsion               |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 0              | 1              |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Skin Abrasion               |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Stress Fracture             |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Thermal Burn                |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Traumatic Haematoma         |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 0              | 1              |
| Cardiac disorders           |                |                |                |
| Bradycardia                 |                |                |                |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 35 (5.71%) | 2 / 37 (5.41%) |
| occurrences (all)           | 3              | 3              | 2              |
| Nervous system disorders    |                |                |                |
| Carpal Tunnel Syndrome      |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 35 (5.71%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 2              | 1              |
| Decreased Vibratory Sense   |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Dizziness                   |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Dizziness Postural          |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 0              | 1              |
| Headache                    |                |                |                |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 35 (2.86%) | 2 / 37 (5.41%) |
| occurrences (all)           | 3              | 1              | 2              |
| Hypoaesthesia               |                |                |                |
| subjects affected / exposed | 2 / 37 (5.41%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)           | 3              | 0              | 0              |
| Paraesthesia                |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 35 (2.86%) | 1 / 37 (2.70%) |
| occurrences (all)           | 1              | 1              | 1              |
| Presyncope                  |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Tremor                      |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Ear and labyrinth disorders |                |                |                |
| Hypoacusis                  |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Vertigo                     |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 2 / 35 (5.71%) | 1 / 37 (2.70%) |
| occurrences (all)           | 1              | 2              | 1              |
| Gastrointestinal disorders  |                |                |                |
| Abdominal Discomfort        |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Diarrhoea                   |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |
| Dyspepsia                   |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Hiatus Hernia               |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 0              | 2              |
| Nausea                      |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Rectal Prolapse             |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Tooth Impacted              |                |                |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0              |
| Toothache                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%)  | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0              |
| Vomiting  |                |                 |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0              |
| Skin and subcutaneous tissue disorders          |                |                 |                |
| Ecchymosis                                      |                |                 |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0              |
| Hyperhidrosis                                   |                |                 |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0              |
| Skin Burning Sensation                          |                |                 |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 0 / 35 (0.00%)  | 0 / 37 (0.00%) |
| occurrences (all)                               | 2              | 0               | 0              |
| Skin Lesion                                     |                |                 |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%)  | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0              |
| Musculoskeletal and connective tissue disorders |                |                 |                |
| Arthralgia                                      |                |                 |                |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 4 / 35 (11.43%) | 0 / 37 (0.00%) |
| occurrences (all)                               | 1              | 5               | 0              |
| Back Pain                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%)  | 2 / 37 (5.41%) |
| occurrences (all)                               | 0              | 1               | 2              |
| Bursitis  |                |                 |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 35 (2.86%)  | 0 / 37 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0              |
| Joint Effusion                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 35 (0.00%)  | 1 / 37 (2.70%) |
| occurrences (all)                               | 0              | 0               | 1              |
| Joint Swelling                                  |                |                 |                |



|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 37 (0.00%) | 2 / 35 (5.71%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 2              | 1              |
| Musculoskeletal Chest Pain  |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Musculoskeletal Pain        |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 3 / 35 (8.57%) | 2 / 37 (5.41%) |
| occurrences (all)           | 2              | 4              | 2              |
| Myalgia                     |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Osteoarthritis              |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 2              | 1              | 0              |
| Pain in Extremity           |                |                |                |
| subjects affected / exposed | 2 / 37 (5.41%) | 2 / 35 (5.71%) | 3 / 37 (8.11%) |
| occurrences (all)           | 2              | 2              | 3              |
| Periarthritis               |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 0 / 35 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 0              | 1              |
| Spinal Osteoarthritis       |                |                |                |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Synovial Cyst               |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Tendonitis                  |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Infections and infestations |                |                |                |
| Acute Sinusitis             |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Bronchitis                  |                |                |                |
| subjects affected / exposed | 0 / 37 (0.00%) | 3 / 35 (8.57%) | 0 / 37 (0.00%) |
| occurrences (all)           | 0              | 3              | 0              |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Conjunctivitis                          |                |                |                |
| subjects affected / exposed             | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |
| Diverticulitis                          |                |                |                |
| subjects affected / exposed             | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 2              | 0              | 0              |
| Gastroenteritis                         |                |                |                |
| subjects affected / exposed             | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Herpes Zoster                           |                |                |                |
| subjects affected / exposed             | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Influenza                               |                |                |                |
| subjects affected / exposed             | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |
| Lower Respiratory Tract Infection       |                |                |                |
| subjects affected / exposed             | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Lower Respiratory Tract Infection Viral |                |                |                |
| subjects affected / exposed             | 0 / 37 (0.00%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 0              | 1              | 0              |
| Nasopharyngitis                         |                |                |                |
| subjects affected / exposed             | 3 / 37 (8.11%) | 1 / 35 (2.86%) | 1 / 37 (2.70%) |
| occurrences (all)                       | 3              | 1              | 1              |
| Pneumonia                               |                |                |                |
| subjects affected / exposed             | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |
| Sinusitis                               |                |                |                |
| subjects affected / exposed             | 1 / 37 (2.70%) | 1 / 35 (2.86%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 1              | 1              | 0              |
| Urinary Tract Infection                 |                |                |                |
| subjects affected / exposed             | 1 / 37 (2.70%) | 0 / 35 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all)                       | 1              | 0              | 0              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 31 October 2014  | Amendment INT-1 included the following changes: assessment for efficacy variables of WOMAC and PGA were added based on health authority feedback for efficacy analysis after discontinuation of treatment; clarification to improve performance of assessments and conduct of study; and minor errors were noted.  |
| 06 February 2015 | Amendment INT-2 included the: Clarification and consistency to labeling and guidelines.  |
| 09 February 2015 | Amendment INT-3 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.  |
| 09 July 2015     | Amendment INT-4 included the following changes: Changes requested by ethics committees and health authorities to clarify study conduct and/or subject; Changes to clarify study conduct.   |
| 14 December 2015 | Amendment INT-5 included the following changes: Respond to regulatory authority request to prohibit resumption of dosing for subjects who develop joint events of interests; 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; clarify that fasting serum and urine samples are preferred for biomarker analysis; and minor errors were noted. |

Notes:

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### 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: