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:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	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.

Arm title	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.

Arm title	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
Arm title	Placebo

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Fulranumab 1 mg

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Fulranumab 3 mg

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Placebo	Fulranumab 1 mg	Fulranumab 3 mg
Started	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
Arm title	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

Arm title	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

Arm title	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

Number of subjects in period 3	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:	
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:	
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 milligram (mg)	Fulranumab 3 mg
Number of subjects	37	35	37
Title for AgeCategorical 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 Units: years			
median	65	61	64
full range (min-max)	49 to 81	43 to 85	38 to 82
Title for Gender Units: subjects			
Female	27	27	16
Male	10	8	21

Reporting group values	Total		
Number of subjects	109		
Title for AgeCategorical 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 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:	
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:	
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 title	Placebo
Reporting group description:	
Subjects who received placebo in treatment phase were followed for 24 weeks in this period.	
Reporting group title	Fulranumab 1 mg
Reporting group description:	
Subjects who received fulranumab 1 mg in treatment phase were followed for 24 weeks in this period.	
Reporting group title	Fulranumab 3 mg
Reporting group description:	
Subjects who received fulranumab 3 mg in treatment phase were followed for 24 weeks in this period.	
Reporting group title	Placebo
Reporting group description:	
Subjects who received placebo in treatment phase were followed for 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:	
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:	
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[1]
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:

[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 (rolephysical, 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[2]	0[3]	0[4]	
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[5]	0[6]	0[7]	
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 %

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

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: