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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	42160443PAI3001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development LLC
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry group, Janssen Research & Development LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry group, Janssen Research & Development LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	43
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

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

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

Dosage and administration details:

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

Arm title	Fulranumab 1 mg

Arm description:

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

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

Dosage and administration details:

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

Arm title	Fulranumab 3 mg

Arm description:

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

Arm type	Experimental

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

Dosage and administration details:

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

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

Period 2

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Fulranumab 1 mg

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Fulranumab 3 mg

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

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

Period 3

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Fulranumab 1 mg

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Fulranumab 3 mg

Arm description:

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

Arm type	No intervention

No investigational medicinal product assigned in this arm

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

Baseline characteristics

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

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

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

Title for Gender Units: subjects			
Female	51		
Male	27		

End points

End points reporting groups

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

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

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

End point type	Primary

End point timeframe:

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this primary end point.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline through Week 20

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline through double-blind Phase

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline through double-Blind Phase

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline through double-blind Phase

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 67 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	FUL 1mg
Reporting group description:	
Subjects received fulranumab 1 mg injection every 4 weeks for 16 weeks during double-blind treatment phase and were followed up for 24 weeks in follow up phase (Period 2).Subjects who received Fulranumab 1mg and discontinued from the double-blind phase and did not enter the post-treatment follow-up phase were followed up for 24 weeks in LSFU phase (Period 3). Subjects who discontinued from the post-treatment follow-up phase were also followed up for 24 weeks in LSFU (Period 3).	
Reporting group title	Placebo
Reporting group description:	
Subjects received 4 placebo subcutaneous (SC) injection (one injection every 4 week) for 16 weeks during double blind treatment phase (Period 1) and were followed up for 24 weeks in follow up phase (Period 2).Subjects who received placebo and discontinued from the double-blind phase and did not enter the post-treatment follow-up phase were followed up for 24 weeks in LSFU phase (Period 3). Subjects who discontinued from the post-treatment follow-up phase were also followed up for 24 weeks in LSFU (Period 3).	
Reporting group title	FUL 3mg
Reporting group description:	
Subjects received fulranumab 1 mg injection every 4 weeks for 16 weeks during double-blind treatment phase and were followed up for 24 weeks in follow up phase (Period 2).Subjects who received Fulranumab 3 mg and discontinued from the double-blind phase and did not enter the post-treatment follow-up phase were followed up for 24 weeks in LSFU phase (Period 3). Subjects who discontinued from the post-treatment follow-up phase were also followed up for 24 weeks in LSFU (Period 3).	

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

subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

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

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

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

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

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

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

subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Tinea Pedis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 26 (3.85%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Urinary Tract Infection			
subjects affected / exposed	2 / 25 (8.00%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	2
Vitamin D Deficiency			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Decreased Appetite			
subjects affected / exposed	1 / 25 (4.00%)	0 / 26 (0.00%)	0 / 27 (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
17 February 2015	Amendment INT-1 included the following changes: Addition of criteria to be used to alert the Independent Data Monitoring Committee (IDMC) to review events of interest (neurologic) and reference to criteria to be used by the IDMC for decisions related to the further conduct of the study based on prespecified safety based criteria (for joint replacement, neurologic, sympathetic, hepatic and renal events of interest, that is stopping criteria).
18 February 2015	Amendment INT-2 included the following changes: Addition of criteria to be used to alert the IDMC to review events of interest (neurologic) and reference to criteria to be used by the IDMC for decisions related to the further conduct of the study based on prespecified safety based criteria (for joint replacement, neurologic, sympathetic, hepatic and renal events of interest, ie, stopping criteria); clarification to improve performance of assessments and conduct of study and minor errors were noted.
16 July 2015	Amendment INT-3 included the following changes: Changes requested by ethics committees and health authorities to clarify study conduct and/or subject safety; and changes to clarify study conduct.
14 December 2015	Amendment INT-4 included the following changes: Respond to regulatory authority request to prohibit resumption of dosing for subjects who develop joint events of interest; respond to regulatory authority requests to include an assessment for carpal tunnel syndrome (CTS), at each clinic visit during the treatment periods, and at dedicated clinic visits during the safety follow-up period; clarification of what is acceptable as opioid failure in U.S. and Canada as per FDA request. clarification that a medication that is contraindicated will qualify as a failure due to intolerability; and clarify that fasting serum and urine samples are preferred for biomarker analysis; and minor errors were noted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: