Clinical trial results:
A Randomized, Double-blind, Multi-dose, Placebo-controlled Phase 2/3 Study to Evaluate the Efficacy and Safety of Fasinumab in Patients With Moderate to Severe Chronic Low Back Pain

Summary

EudraCT number	2015-003782-28
Trial protocol	DK CZ PL HU
Global end of trial date	13 September 2017

Results information

Result version number	v1
This version publication date	30 September 2018
First version publication date	30 September 2018

Trial information

Trial identification

Sponsor protocol code	R475-PN-1524

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02620020
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591
Public contact	Clinical Trial Management , Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management , Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.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	18 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of fasinumab compared to placebo in reducing low back pain (LBP) as measured by the change from baseline to Week 16 in the average daily low back pain intensity (LBPI) numeric rating scale (NRS) score.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 92
Country: Number of subjects enrolled	Czech Republic: 63
Country: Number of subjects enrolled	Denmark: 76
Country: Number of subjects enrolled	Estonia: 12
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	United States: 286
Country: Number of subjects enrolled	Canada: 3
Worldwide total number of subjects	563
EEA total number of subjects	274

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)	414
From 65 to 84 years	147
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 105 sites in the US, CA & EU between 26 Jan 2016 & 13 Sep 2017. Of 1,783 subjects, 563 were randomized in 1:1:1:1 ratio to 1 of 4 treatment groups stratified by baseline LBPI, NRS score (<7, ≥7), duration of chronic LBP (<5 yrs, ≥5yrs) & maximum Kellgren-Lawrence (K-L) score (≤2, >2) at any knee or hip joint at screening.

Pre-assignment

Screening details:

The study consisted of a screening period of up to 30 days & a 7-day pre-randomization period during which pain medication, except study-provided rescue medication, was discontinued. Confirmation of no exclusionary findings on joint on which imaging was performed during screening must have been received before a subject could be randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo SC Q4W and Placebo IV Q8W

Arm description:

Subjects randomized to the matching placebo subcutaneously (SC) every four weeks (Q4W) arm received SC placebo in a manner similar to the SC loading dose of the active groups (placebo loading dose) on Day 1 and then an SC injection of placebo at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo intravenously (IV) every 8 weeks (Q8W) was received on Day 1 and at Week 8.

Arm type	Placebo
Investigational medicinal product name	Placebo IV (Matching to Fasinumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of placebo (matching to fasinumab) on Day 1 and at Week 8.

Investigational medicinal product name	Placebo SC (Matching to Fasinumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received SC injection of placebo (matching to fasinumab) on Day 1, and at Week 4, 8, 12.

Arm title	Fasinumab 6 mg SC Q4W and Placebo IV Q8W

Arm description:

Subjects randomized to the fasinumab 6 mg SC Q4W arm received fasinumab 12 mg SC on Day 1 (loading dose) and then 6 mg SC (planned maintenance dose) at Weeks 4, 8, and 12 for a total of 4 doses. Matching placebo was received via intravenous (IV) infusion Q8W on Day 1 and at Week 8.

Arm type	Experimental

Investigational medicinal product name	Fasinumab
Investigational medicinal product code	REGN475
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received SC injection of fasinumab on Day 1, and at Week 4, 8, 12.

Investigational medicinal product name	Placebo (Matching to Fasinumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of placebo (matching to fasinumab) on Day 1 and at Week 8.

Arm title	Fasinumab 9 mg SC Q4W and Placebo IV Q8W

Arm description:

Subjects randomized to the fasinumab 9 mg SC Q4W arm received 18 mg SC on day 1 (loading dose) and then 9 mg SC (planned maintenance dose) at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8.

Arm type	Experimental
Investigational medicinal product name	Fasinumab
Investigational medicinal product code	REGN475
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received SC injection of fasinumab on Day 1, and at Week 4, 8, 12.

Investigational medicinal product name	Placebo (Matching to Fasinumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of placebo (matching to fasinumab) on Day 1 and at Week 8.

Arm title	Fasinumab 9 mg IV Q8W and Placebo SC Q4W

Arm description:

Subjects randomized to the fasinumab 9 mg IV Q8W arm received IV infusions of fasinumab 9 mg on Day 1 and Week 8, for a total of 2 doses. Matching placebo SC Q4W was received on day 1 and at weeks 4, 8, and 12.

Arm type	Experimental
Investigational medicinal product name	Fasinumab
Investigational medicinal product code	REGN475
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subject received IV infusion of fasinumab on Day 1, and at Week 8.

Investigational medicinal product name	Placebo (Matching to Fasinumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection

Routes of administration	Subcutaneous use

Dosage and administration details:

Subject received SC injection of placebo (matching to fasinumab) on Day 1, and at Week 4, 8, 12.

Number of subjects in period 1	Placebo SC Q4W and Placebo IV Q8W	Fasinumab 6 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg SC Q4W and Placebo IV Q8W
Started	141	141	140
Completed	97	106	115
Not completed	44	35	25
Physician decision	7	4	3
Consent withdrawn by subject	20	16	17
Death	-	1	-
Adverse event	8	4	3
Lost to follow-up	4	8	1
Protocol deviation	5	2	1

Number of subjects in period 1	Fasinumab 9 mg IV Q8W and Placebo SC Q4W
Started	141
Completed	115
Not completed	26
Physician decision	4
Consent withdrawn by subject	12
Death	-
Adverse event	5
Lost to follow-up	4
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the matching placebo subcutaneously (SC) every four weeks (Q4W) arm received SC placebo in a manner similar to the SC loading dose of the active groups (placebo loading dose) on Day 1 and then an SC injection of placebo at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo intravenously (IV) every 8 weeks (Q8W) was received on Day 1 and at Week 8.

Reporting group title	Fasinumab 6 mg SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the fasinumab 6 mg SC Q4W arm received fasinumab 12 mg SC on Day 1 (loading dose) and then 6 mg SC (planned maintenance dose) at Weeks 4, 8, and 12 for a total of 4 doses. Matching placebo was received via intravenous (IV) infusion Q8W on Day 1 and at Week 8.

Reporting group title	Fasinumab 9 mg SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the fasinumab 9 mg SC Q4W arm received 18 mg SC on day 1 (loading dose) and then 9 mg SC (planned maintenance dose) at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8.

Reporting group title	Fasinumab 9 mg IV Q8W and Placebo SC Q4W

Reporting group description:

Subjects randomized to the fasinumab 9 mg IV Q8W arm received IV infusions of fasinumab 9 mg on Day 1 and Week 8, for a total of 2 doses. Matching placebo SC Q4W was received on day 1 and at weeks 4, 8, and 12.

Reporting group values	Placebo SC Q4W and Placebo IV Q8W	Fasinumab 6 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg SC Q4W and Placebo IV Q8W
Number of subjects	141	141	140
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.1	58.2	56.6
standard deviation	± 12.54	± 11.29	± 10.99
Gender categorical Units: Subjects			
Female	83	85	84
Male	58	56	56
Ethnicity Units: Subjects			
Hispanic or Latino	7	4	4
Not Hispanic or Latino	134	135	135
Not Reported	0	2	1
Race Units: Subjects			
White	127	119	118
Black or African American	13	19	19
Asian	1	2	2

American Indian or Alaska Native	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	1

Reporting group values	Fasinumab 9 mg IV Q8W and Placebo SC Q4W	Total	
Number of subjects	141	563	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	55.4		
standard deviation	± 10.49	-	
Gender categorical			
Units: Subjects			
Female	81	333	
Male	60	230	
Ethnicity			
Units: Subjects			
Hispanic or Latino	10	25	
Not Hispanic or Latino	131	535	
Not Reported	0	3	
Race			
Units: Subjects			
White	116	480	
Black or African American	21	72	
Asian	1	6	
American Indian or Alaska Native	1	2	
Native Hawaiian or Other Pacific Islander	1	1	
Other	1	2	

End points

End points reporting groups

Reporting group title	Placebo SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the matching placebo subcutaneously (SC) every four weeks (Q4W) arm received SC placebo in a manner similar to the SC loading dose of the active groups (placebo loading dose) on Day 1 and then an SC injection of placebo at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo intravenously (IV) every 8 weeks (Q8W) was received on Day 1 and at Week 8.

Reporting group title	Fasinumab 6 mg SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the fasinumab 6 mg SC Q4W arm received fasinumab 12 mg SC on Day 1 (loading dose) and then 6 mg SC (planned maintenance dose) at Weeks 4, 8, and 12 for a total of 4 doses. Matching placebo was received via intravenous (IV) infusion Q8W on Day 1 and at Week 8.

Reporting group title	Fasinumab 9 mg SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the fasinumab 9 mg SC Q4W arm received 18 mg SC on day 1 (loading dose) and then 9 mg SC (planned maintenance dose) at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8.

Reporting group title	Fasinumab 9 mg IV Q8W and Placebo SC Q4W

Reporting group description:

Subjects randomized to the fasinumab 9 mg IV Q8W arm received IV infusions of fasinumab 9 mg on Day 1 and Week 8, for a total of 2 doses. Matching placebo SC Q4W was received on day 1 and at weeks 4, 8, and 12.

Primary: Change From Baseline in the Average Daily Low Back Pain Intensity (LBPI) Score on an 11-point Numerical Rating Scale (NRS) at Week 16

End point title	Change From Baseline in the Average Daily Low Back Pain Intensity (LBPI) Score on an 11-point Numerical Rating Scale (NRS) at Week 16

End point description:

Average daily low back pain was assessed on an 11-point numeric rating scale (NRS) and was defined as the average of the non-missing daily LBPI NRS scores for the 7 days before and including nominal visit. Subjects described their average low back pain during the past 24 hours on a scale ranging from 0 (no pain) to 10 (worst possible pain), where higher scores indicate higher pain. Analysis was performed on modified intent to treat set (mITT) that included all randomized subject per Interactive voice response system (IVRS) who received at least one dose of study drug based on the treatment allocated (as randomized) including data up to 5 weeks after the last dose of study drug. Here, number of subjects analyzed=subjects with available data for specified timepoint.

End point type	Primary

End point timeframe:

Baseline, Week 16

End point values	Placebo SC Q4W and Placebo IV Q8W	Fasinumab 6 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg IV Q8W and Placebo SC Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	48	55	56
Units: Units on a scale				
least squares mean (standard error)	-1.7 (± 0.23)	-2.0 (± 0.23)	-2.5 (± 0.22)	-2.4 (± 0.22)

Statistical analyses

Statistical analysis title	Fasinumab 6 mg SC Q4W vs Placebo
Statistical analysis description:	
Analyses are based on mixed-effect model repeated measures (MMRM) model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.	
Comparison groups	Fasinumab 6 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3876
Method	Mixed-effect model analysis
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.31

Statistical analysis title	Fasinumab 9 mg SC Q4W vs Placebo
Statistical analysis description:	
Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.	
Comparison groups	Fasinumab 9 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Mixed-effect model analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	Fasinumab 9 mg IV Q8W and placebo

Statistical analysis description:

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

Comparison groups	Fasinumab 9 mg IV Q8W and Placebo SC Q4W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0288
Method	Mixed-effect model analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.3

Secondary: Change From Baseline in the Roland Morris Disability Questionnaire (RMDQ) Total Score at Week 16

End point title	Change From Baseline in the Roland Morris Disability Questionnaire (RMDQ) Total Score at Week 16

End point description:

The RMDQ is a self-administered, widely used health status measure for LBP. It measures pain and function, using 24 items describing limitations to everyday life that can be caused by LBP. The score of the RMDQ is the total number of items checked – that is from a minimum of 0 (no disability) to a maximum of 24 (maximum disability), where lower scores indicative of better function. Analysis was performed on mITT population. Here, number of subjects analyzed=subjects with available data for specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo SC Q4W and Placebo IV Q8W	Fasinumab 6 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg IV Q8W and Placebo SC Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	46	55	55
Units: Units on a scale				
least squares mean (standard error)	-3.8 (± 0.54)	-6.0 (± 0.54)	-5.8 (± 0.51)	-6.3 (± 0.51)

Statistical analyses

Statistical analysis title	Fasinumab 6 mg SC Q4W vs Placebo
Statistical analysis description:	
Analyses are based on mixed-effect model repeated measures (MMRM) model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.	
Comparison groups	Fasinumab 6 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0028
Method	Mixed-effect model analysis
Parameter estimate	LS mean difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.65
upper limit	-0.77
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	Fasinumab 9 mg SC Q4W vs Placebo
Statistical analysis description:	
Analyses are based on mixed-effect model repeated measures (MMRM) model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.	
Comparison groups	Fasinumab 9 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068
Method	Mixed-effect model analysis
Parameter estimate	LS Mean Difference
Point estimate	-2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.36
upper limit	-0.54
Variability estimate	Standard error of the mean
Dispersion value	0.72

Statistical analysis title	Fasinumab 9 mg IV Q8W and placebo

Statistical analysis description:

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

Comparison groups	Fasinumab 9 mg IV Q8W and Placebo SC Q4W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Mixed-effect model analysis
Parameter estimate	LS Mean Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.88
upper limit	-1.06
Variability estimate	Standard error of the mean
Dispersion value	0.72

Secondary: Change From Baseline in the Patient Global Assessment (PGA) of Low Back Pain (LBP) Score at Week 16

End point title	Change From Baseline in the Patient Global Assessment (PGA) of Low Back Pain (LBP) Score at Week 16

End point description:

The PGA of LBP is a patient assessed 5 point Likert scale of LBP ranging from 0-5 where 1=very well; 2=well; 3=fair; 4=poor; and 5=very poor. Analysis was performed on mITT population. Here, number of subjects analyzed=subjects with available data for specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo SC Q4W and Placebo IV Q8W	Fasinumab 6 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg IV Q8W and Placebo SC Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	48	55	57
Units: Units on a scale				
least squares mean (standard error)	-0.7 (± 0.10)	-0.9 (± 0.10)	-0.8 (± 0.10)	-1.0 (± 0.09)

Statistical analyses

Statistical analysis title	Fasinumab 6 mg SC Q4W vs Placebo
Statistical analysis description:	
Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.	
Comparison groups	Fasinumab 6 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1501
Method	Mixed-effect model analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Fasinumab 9 mg SC Q4W vs Placebo
Statistical analysis description:	
Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.	
Comparison groups	Fasinumab 9 mg SC Q4W and Placebo IV Q8W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2603
Method	Mixed-effect model analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Fasinumab 9 mg IV Q8W and placebo

Statistical analysis description:

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

Comparison groups	Fasinumab 9 mg IV Q8W and Placebo SC Q4W v Placebo SC Q4W and Placebo IV Q8W
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed-effect model analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.13

Secondary: Change From Baseline in Low Back Pain Intensity (LBPI) Numerical Rating Scale (NRS) Score at Weeks 2, 4, 8, and 12

End point title	Change From Baseline in Low Back Pain Intensity (LBPI) Numerical Rating Scale (NRS) Score at Weeks 2, 4, 8, and 12

End point description:

Low back pain intensity was assessed on an 11-point numeric rating scale (NRS) and was defined as the average of the non-missing daily LBPI NRS scores for the 7 days before and including nominal visit. Subjects described their average low back pain during the past 24 hours on a scale ranging from 0 (no pain) to 10 (worst possible pain), where higher scores indicate higher pain. Analysis was performed on modified intent to treat set mITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline and at Week 2, 4, 8, and 12

End point values	Placebo SC Q4W and Placebo IV Q8W	Fasinumab 6 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg IV Q8W and Placebo SC Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140	139	139	140
Units: Units on a scale				
least squares mean (standard error)				
Change at Week 2 (n = 136, 133, 135, 138)	-0.9 (± 0.17)	-1.3 (± 0.17)	-1.6 (± 0.17)	-1.6 (± 0.16)
Change at Week 4 (n = 133, 132, 128, 132)	-0.9 (± 0.17)	-1.5 (± 0.17)	-2.0 (± 0.17)	-1.9 (± 0.16)
Change at Week 8 (n = 95, 98, 105, 103)	-1.2 (± 0.19)	-1.8 (± 0.19)	-2.3 (± 0.19)	-2.2 (± 0.19)
Change at Week 12 (n = 69, 69, 74, 76)	-1.5 (± 0.21)	-2.0 (± 0.21)	-2.6 (± 0.21)	-2.5 (± 0.21)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Week 36) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment emergent that is AEs that developed/worsened and deaths that occurred during 'the treatment emergent period' (from the first dose of study drug up to the 4 weeks after the last dose of SC drug, or 8 weeks after the last dose of IV study drug, whichever is later).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the matching placebo SC Q4W arm received SC placebo in a manner similar to the SC loading dose of the active groups (placebo loading dose) on Day 1 and then an SC injection of placebo at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8.

Reporting group title	Fasinumab 6 mg SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the fasinumab 6 mg SC Q4W arm received fasinumab 12 mg SC on Day 1 (loading dose) and then 6 mg SC (planned maintenance dose) at Weeks 4, 8, and 12 for a total of 4 doses. Matching placebo was received via intravenous (IV) infusion Q8W on Day 1 and at Week 8.

Reporting group title	Fasinumab 9 mg SC Q4W and Placebo IV Q8W

Reporting group description:

Subjects randomized to the fasinumab 9 mg SC Q4W arm received 18 mg SC on day 1 (loading dose) and then 9 mg SC (planned maintenance dose) at weeks 4, 8, and 12 for a total of 4 doses. Matching placebo IV Q8W was received on Day 1 and at Week 8.

Reporting group title	Fasinumab 9 mg IV Q8W and Placebo SC Q4W

Reporting group description:

Subjects randomized to the fasinumab 9 mg IV Q8W arm received IV infusions of fasinumab 9 mg on Day 1 and Week 8, for a total of 2 doses. Matching placebo SC Q4W was received on day 1 and at weeks 4, 8, and 12.

Serious adverse events	Placebo SC Q4W and Placebo IV Q8W	Fasinumab 6 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg SC Q4W and Placebo IV Q8W
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 140 (2.86%)	2 / 139 (1.44%)	3 / 139 (2.16%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 140 (0.71%)	0 / 139 (0.00%)	0 / 139 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 140 (0.00%)	0 / 139 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue carcinoma stage iv			
subjects affected / exposed	1 / 140 (0.71%)	0 / 139 (0.00%)	0 / 139 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 140 (0.00%)	1 / 139 (0.72%)	0 / 139 (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
Craniocerebral injury			
subjects affected / exposed	0 / 140 (0.00%)	1 / 139 (0.72%)	0 / 139 (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
Eye injury			
subjects affected / exposed	1 / 140 (0.71%)	0 / 139 (0.00%)	0 / 139 (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
Meniscus injury			
subjects affected / exposed	0 / 140 (0.00%)	0 / 139 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 140 (0.00%)	0 / 139 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skull fracture			
subjects affected / exposed	0 / 140 (0.00%)	1 / 139 (0.72%)	0 / 139 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 140 (0.00%)	0 / 139 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 140 (0.00%)	1 / 139 (0.72%)	0 / 139 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 140 (0.71%)	0 / 139 (0.00%)	0 / 139 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 140 (0.00%)	0 / 139 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 140 (0.00%)	0 / 139 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 140 (0.00%)	0 / 139 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Diverticulitis			
subjects affected / exposed	0 / 140 (0.00%)	0 / 139 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Fasinumab 9 mg IV Q8W and Placebo SC Q4W		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 140 (3.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue carcinoma stage iv			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye injury			

subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus injury			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull fracture			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo SC Q4W and Placebo IV Q8W	Fasinumab 6 mg SC Q4W and Placebo IV Q8W	Fasinumab 9 mg SC Q4W and Placebo IV Q8W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 140 (31.43%)	35 / 139 (25.18%)	52 / 139 (37.41%)
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 140 (6.43%)	9 / 139 (6.47%)	9 / 139 (6.47%)
occurrences (all)	11	9	19
Hypoaesthesia			
subjects affected / exposed	4 / 140 (2.86%)	4 / 139 (2.88%)	7 / 139 (5.04%)
occurrences (all)	4	4	7
Paraesthesia			
subjects affected / exposed	4 / 140 (2.86%)	6 / 139 (4.32%)	9 / 139 (6.47%)
occurrences (all)	4	6	9
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 140 (1.43%)	4 / 139 (2.88%)	7 / 139 (5.04%)
occurrences (all)	4	4	7

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 140 (12.14%)	15 / 139 (10.79%)	16 / 139 (11.51%)
occurrences (all)	20	19	18
Back pain			
subjects affected / exposed	7 / 140 (5.00%)	0 / 139 (0.00%)	4 / 139 (2.88%)
occurrences (all)	7	0	4
Pain in extremity			
subjects affected / exposed	12 / 140 (8.57%)	3 / 139 (2.16%)	5 / 139 (3.60%)
occurrences (all)	13	4	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 140 (5.71%)	9 / 139 (6.47%)	8 / 139 (5.76%)
occurrences (all)	8	9	9

Non-serious adverse events	Fasinumab 9 mg IV Q8W and Placebo SC Q4W		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 140 (35.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 140 (6.43%)		
occurrences (all)	9		
Hypoaesthesia			
subjects affected / exposed	3 / 140 (2.14%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	9 / 140 (6.43%)		
occurrences (all)	9		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 140 (15.00%)		
occurrences (all)	21		

Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 5 / 140 (3.57%) 5 4 / 140 (2.86%) 6		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 10 / 140 (7.14%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2016	Following changes were made: - Clarified that the maximum dose of paracetamol/acetaminophen permitted as rescue medication for LBP is 2,600 mg (325 mg x 8) per day in North America, and 2,500 mg (500 mg x 5) per day in Europe, - added confirmed elevated screening ALT or AST > 2.5 x upper limit of normal (ULN) as an exclusion criterion, - added continued noncompliance with protocol-defined maximum paracetamol/acetaminophen use after appropriate counseling as a reason for permanent discontinuation of study drug, - changed the notification requirement for emergency unblinding to "The investigator should promptly document and explain to the sponsor any premature unblinding." - Made administrative edits.
20 January 2016	Following changes were made: - Incorporated revisions to ensure a consistent approach across the fasinumab program, for imaging requirements: added further detail on imaging requirements during the screening period, - specified that radiographs and/or MRI will or must (rather than should) be performed on any joint following report of a clinically significant worsening or exacerbation of pain in that joint, - specified that prior to the pre-randomization visit, - an MRI of the affected joint must be performed and assessed by the central reader for any screening radiographs that are inconclusive for potential joint-related findings and for any knee or hip joint that has a baseline K-L score of ≥3, and specified that, before a subject was randomized, confirmation must be received that there are no exclusionary finding on screening MRIs, - updated the study stopping rules to state that the DMC may recommend temporarily halting the study if the DMC has significant concerns regarding a meaningful imbalance in joint-related AEs, SNS dysfunction, or neurosensory disturbances, - added willingness to consider TJR if necessary as an inclusion criterion, modified exclusion criteria, - added clinically significant sensory and motor neurologic events grade >2 according to Common Terminology Criteria for Adverse Events (CTCAE) v.4 as a new reason for permanent discontinuation of study drug; - specified that sites should use CTCAE v.4 criteria throughout the study for consistency, - added new signs and symptoms indicative of carpal tunnel syndrome as a new reason for permanent discontinuation of study drug, - modified schedule of events, - study visit descriptions and study procedures, - refined and further detail text describing safety reporting, - and monitoring of adverse events of special interest (AESI), - refined and further detail the statistical plan, made minor clarifications and administrative edits.
26 August 2016	Following changes were made: - Added additional collection time points for urine to better monitor patient safety, - added creatinine and phosphorous to routine serum and urine chemistry sampling to better monitor patient safety, - updated the terminology from "destructive arthropathy" to "adjudicated arthropathy" to allow for consistency within the program and to allow for a more accurate description of the joint events in the trial, - updated the personnel who have the authorization to approve rescreening, - updated the reporting time for AESIs from 7 days to 24 hours.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

14 October 2016	The Food and Drug Administration (FDA) placed the study on partial clinical hold following an adjudicated arthropathy (AA) event that occurred in a subject with chronic low back pain (LBP) and a history of advanced osteoarthritis (OA) (K-L = 3 in the AA joint at screening).	-

Notes:

Limitations and caveats

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

As a result of the partial clinical hold the Sponsor made a decision not to amend the protocol and consequently randomization and dosing was prematurely discontinued.

Notes: