Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-42160443 as Adjunctive Therapy in Subjects With Cancer-Related Pain, Followed by an Open-Label Extension Phase

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2008-007690-21
Trial protocol	FR ES PT IT NL
Global end of trial date	19 January 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	42160443PAI2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00929188
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	Antwerpseweg 15-17, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen Research and Development, Clinical Registry Group, Janssen Research and Development, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research and Development, Clinical Registry Group, Janssen Research and Development, 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 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the analgesic efficacy, safety, and tolerability of a single subcutaneous (SC) dose [9 milligram (mg) in 0.3 milliliter (mL)] of JNJ-42160443 compared with placebo as adjunctive therapy to standard pain therapy in subjects with inadequately controlled, moderate to severe, chronic, cancer-related pain. This study was an adjunctive trial with the addition of fulranumab to pre-existing inadequate analgesia regimen; the Double-Blind period was 1 month in duration with 1 dose of study medication.

Protection of trial subjects:

Safety evaluations included the collection of adverse events, clinical laboratory tests (including Serum chemistry, hematology, urinalysis and serum pregnancy test), vital signs, physical examinations, Electrocardiograms, Injection-Site Evaluations, Neurologic Examination and Assessment of Joint Safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2009
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	Spain: 16
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Portugal: 14
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	98
EEA total number of subjects	54

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)	71
From 65 to 84 years	26
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 22 sites in 4 countries from 24 September 2009 to 19 January 2015. Other countries (for example, Italy and
Netherlands) are not included in trial information as no subjects were enrolled in these countries.

Pre-assignment

Screening details:

98 subjects were analyzed in the double-blind phase out of which 71 subjects were entered into open-label phase

Period 1

Period 1 title	Double-Blind Treatment Phase
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

Arm description:

Subjects received placebo subcutaneous (SC) injection once on Day 1 in Double-blind treatment phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received placebo subcutaneous (SC) injection once on Day 1 in Double-blind treatment phase.

Arm title	Fulranumab

Arm description:

Subjects received Fulranumab [9 milligram (mg) in 0.9 millilitre (mL)] SC once on Day 1 in Double-blind treatment phase.

Arm type	Experimental
Investigational medicinal product name	Fulranumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received Fulranumab [9 milligram (mg) in 0.9 millilitre (mL)] SC once on Day 1 in Double-blind treatment phase.

Number of subjects in period 1	Placebo	Fulranumab
Started	31	67
Completed	29	54
Not completed	2	13
Physician decision	1	1
Consent withdrawn by subject	1	1
Adverse serious fatal	-	8
Adverse event	-	3

Period 2	
Period 2 title	Open-Label Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Fulranumab

Arm description:

Subjects received Fulranumab (9 mg in 0.9 mL) SC once every 4 weeks for a maximum of 12 doses in Open-label phase

Arm type	Experimental
Investigational medicinal product name	Fulranumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received Fulranumab (9 mg in 0.9 mL) SC once every 4 weeks for a maximum of 12 doses in Open-label phase

Number of subjects in period 2[1]	Fulranumab
Started	71
Completed	6
Not completed	65
Consent withdrawn by subject	10
Sponsor discontinued cohort/ study	3
Adverse event, non-fatal	6
Death	32
Other	7

Unknown	1
Investigator decision	6

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Please note that the subjects enrolled in the open label period is not the same as of Double bling treatment period.
Subjects who completed the double-blind treatment phase were eligible to enter the open-label extension phase, based on the judgment of the investigator and consistent with subject safety.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo subcutaneous (SC) injection once on Day 1 in Double-blind treatment phase.	
Reporting group title	Fulranumab
Reporting group description:	
Subjects received Fulranumab [9 milligram (mg) in 0.9 millilitre (mL)] SC once on Day 1 in Double-blind treatment phase.	

Reporting group values	Placebo	Fulranumab	Total
Number of subjects	31	67	98
Title for AgeCategorical			
Units: subjects			
Adults (18-64 years)	23	48	71
From 65 to 84 years	8	18	26
85 years and over	0	1	1
Title for AgeContinuous			
Units: years			
arithmetic mean	56.1	59.4	
standard deviation	± 12.12	± 10.73	-
Title for Gender			
Units: subjects			
Female	10	32	42
Male	21	35	56

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo subcutaneous (SC) injection once on Day 1 in Double-blind treatment phase.	
Reporting group title	Fulranumab
Reporting group description:	
Subjects received Fulranumab [9 milligram (mg) in 0.9 millilitre (mL)] SC once on Day 1 in Double-blind treatment phase.	
Reporting group title	Fulranumab
Reporting group description:	
Subjects received Fulranumab (9 mg in 0.9 mL) SC once every 4 weeks for a maximum of 12 doses in Open-label phase	
Subject analysis set title	Intent to treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomly assigned subjects who had received the single injection of fulranumab or placebo in the double-blind treatment phase.	

Primary: Change in Average Cancer-Related Pain Intensity Score From Baseline to end of Double Blind Phase (LOCF)

End point title	Change in Average Cancer-Related Pain Intensity Score From Baseline to end of Double Blind Phase (LOCF)
End point description:	
Average cancer-related pain intensity score is defined as the difference between the value at the end of the double-blind phase and the baseline value. Subjects were asked to assess the average pain intensity on a 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (maximum pain imaginable) by selecting a number applicable to their pain on the scale. Here, data is collected by last observation carried forward (LOCF) approach.	
End point type	Primary
End point timeframe:	
Baseline and End of double blind phase (Week 4)	

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[1]	67[2]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	6.4 (± 1.36)	5.9 (± 1.56)		
Change from Baseline	-0.7 (± 1.56)	-0.8 (± 1.26)		

Notes:

[1] - ITT population

[2] - ITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fulranumab

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.592
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.3

Primary: Change in Average Cancer-Related Pain Intensity Score From Baseline to End of 28 days of Double Blind Phase (LOCF)

End point title	Change in Average Cancer-Related Pain Intensity Score From Baseline to End of 28 days of Double Blind Phase (LOCF)

End point description:

Average cancer-related pain intensity score is defined as the difference between the value at the end of the double-blind phase and the baseline value. Subjects were asked to assess the average pain intensity on a 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (maximum pain imaginable) by selecting a number applicable to their pain on the scale. Here, data is collected by last observation carried forward (LOCF) approach.

End point type	Primary

End point timeframe:

Baseline and Day 28 of Double bling phase

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[3]	67[4]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	6.4 (± 1.36)	5.9 (± 1.56)		
Change from Baseline	-0.8 (± 1.55)	-0.9 (± 1.29)		

Notes:

[3] - ITT Population

[4] - ITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fulranumab

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.576
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.3

Primary: Change in Average Cancer-Related Pain Intensity Score From Baseline to Week 1, 2, 3, and 4

End point title	Change in Average Cancer-Related Pain Intensity Score From Baseline to Week 1, 2, 3, and 4[5]

End point description:

Average cancer-related pain intensity score is defined as the difference between the value at the end of the double-blind phase and the baseline value. Subjects were asked to assess the average pain intensity on a 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (maximum pain imaginable) by selecting a number applicable to their pain on the scale. Here, data is collected for baseline and Week 1, 2, 3 and 4. Here 'n' signifies number of subjects analyzed at specific timepoint

End point type	Primary

End point timeframe:

Baseline and Week 1, 2 ,3 and 4 of Double bling phase

Notes:

[5] - 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: Statistical analysis was not reported for this endpoint as inferential analysis was not performed as planned.

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[6]	67[7]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	6.44 (± 1.357)	5.93 (± 1.564)		
Change from Baseline at week 1 (n=30,59)	-0.44 (± 1.139)	-0.63 (± 1.025)		
Change from Baseline at week 2 (n=29,58)	-0.62 (± 1.253)	-0.88 (± 1.492)		
Change from Baseline at week 3 (n=28,58)	-0.88 (± 1.432)	-0.86 (± 1.324)		
Change from Baseline at week 4 (n=28,55)	-0.95 (± 1.443)	-1 (± 1.375)		

Notes:

[6] - ITT population

[7] - ITT population

Statistical analyses

No statistical analyses for this end point

Primary: Change in Average Cancer-Related Pain Intensity Score From Baseline to Overall Double Blind Phase

End point title	Change in Average Cancer-Related Pain Intensity Score From Baseline to Overall Double Blind Phase

End point description:

Average cancer-related pain intensity score is defined as the difference between the value at the end of the double-blind phase and the baseline value. Subjects were asked to assess the average pain intensity on a 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (maximum pain imaginable) by selecting a number applicable to their pain on the scale. Here, data is collected for baseline and overall double blind phase. Here 'n' signifies number of subjects analyzed at specific timepoint

End point type	Primary

End point timeframe:

Baseline and Double bling phase (Week 4)

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[8]	67[9]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=31,60)	6.4 (± 1.36)	6 (± 1.59)		
Change from Baseline (n=31,60)	-0.6 (± 1.23)	-0.8 (± 1.14)		

Notes:

[8] - ITT population

[9] - ITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Fulranumab
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.189
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.26

Secondary: Percentage of Subjects With Average Cancer-Related Pain Intensity Score Responder (15 Percent(%), 20% , 30% and 50% Improvement)

End point title	Percentage of Subjects With Average Cancer-Related Pain Intensity Score Responder (15 Percent(%), 20% , 30% and 50% Improvement)

End point description:

Responder is defined as the percent improvement in the average cancer-related pain intensity score reaching a given threshold value of 15%, 20% ,30% and 50% at the end of 28-day DB phase. Here 'n' signifies number of subjects analyzed at specific timepoint

End point type	Secondary

End point timeframe:

Baseline and Double Blind Phase (Week 4)

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[10]	67[11]		
Units: percentage of subjects				
number (not applicable)				
Responder rate >= 15 % (n=13,29)	41.9	43.3		
Responder rate >= 20 % (n=10,26)	32.3	38.8		
Responder rate <30% (n=28,46)	90.3	68.7		
Responder rate >=30% (n=03,21)	9.7	31.3		
Responder rate <50% (n=28,61)	90.3	91		
Responder rate >= 50% (n=3,6)	9.7	9		

Notes:

[10] - ITT population

[11] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brief Pain Inventory – Short Form (BPI-SF) Pain Intensity and Pain Interference Subscale Score

End point title	Change From Baseline in Brief Pain Inventory – Short Form (BPI-SF) Pain Intensity and Pain Interference Subscale Score

End point description:

The BPI-sf consists of 15 Items (Item 1:presence of pain; Item 2:pain location; Items 3 to 6:pain severity; Item 7:status of pain treatment; Item 8:efficacy of pain treatment; and Items 9a to 9g: interference of pain with daily life). Pain interference sub-scale score ranges from 0 (do not interfere) to 10 (completely interferes). Higher scores indicates worsening. Total score is defined as the mean scores from Items 3, 4, 5, 6 and 9 recorded on an 11-point scale where 0 = no pain and 10 = pain as bad as you can imagine. Lower score indicates an improvement in pain. Here 'n' signifies number of subjects analyzed at specific timepoint

End point type	Secondary

End point timeframe:

Baseline and End of double blind phase (4 Weeks)

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[12]	67[13]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline in Pain Intensity Subscale (n=30,64)	5.8 (± 1.92)	5.5 (± 1.57)		
Change from Baseline (n=30,64)	0.1 (± 1.91)	-0.7 (± 1.21)		
Baseline in Pain Interference Subscale(n=30,64)	5.8 (± 2.28)	6.2 (± 2.06)		
Change from Baseline(n=30,64)	0.2 (± 2.25)	-1 (± 1.61)		

Notes:

[12] - ITT population

[13] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Participant Global Impression of Change (PGIC)

End point title	Participant Global Impression of Change (PGIC)

End point description:

The Participant Global Impression of Change (PGIC) is a single-item questionnaire designed to provide an overall assessment of treatment from the participant's perspective since the start of the study. It is measured on a 7-point scale, where 1=very much improved and 7=very much worse. A participant is considered a responder if they have a response of "very much improved" or "much improved". Here 'n' signifies number of subjects analyzed at specific timepoint

End point type	Secondary

End point timeframe:

Baseline and End of double blind phase (4 Weeks)

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[14]	67[15]		
Units: Units on a scale				
arithmetic mean (standard deviation)	3.6 (± 1.5)	3.3 (± 1.28)		

Notes:

[14] - ITT population

[15] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Right Now Cancer-related Pain Intensity Score

End point title	Change From Baseline in Right Now Cancer-related Pain Intensity Score

End point description:

Here, data is collected by last observation carried forward (LOCF) approach.

End point type	Secondary

End point timeframe:

Baseline and End of double blind phase (4 Weeks)

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[16]	67[17]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	6.3 (± 1.7)	5.9 (± 1.45)		
Change from baseline	-0.6 (± 1.7)	-0.9 (± 1.3)		

Notes:

[16] - ITT population

[17] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Worst Cancer-Related Pain Intensity Score

End point title	Change From Baseline in Worst Cancer-Related Pain Intensity Score

End point description:

Here, data is collected by last observation carried forward (LOCF) approach.

End point type	Secondary

End point timeframe:

Baseline and End of double blind phase (4 Weeks)

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[18]	67[19]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	7.4 (± 1.34)	7.2 (± 1.29)		
Change from baseline	-0.9 (± 1.58)	-1 (± 1.5)		

Notes:

[18] - ITT population

[19] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Total Opioid use During the Double-Blind Phase

End point title	Total Opioid use During the Double-Blind Phase

End point description:

Here 'n' signifies number of subjects analyzed at specific timepoint. Data is collected by last observation carried forward (LOCF) approach.

End point type	Secondary

End point timeframe:

Baseline and End of double blind phase (4 Weeks)

End point values	Placebo	Fulranumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[20]	67[21]		
Units: Milligram				
arithmetic mean (standard deviation)				
Baseline (n=29,67)	405.2 (± 682.44)	381.5 (± 607.78)		
Change from baseline (n=29,67)	-26.9 (± 99.16)	4.6 (± 295.37)		

Notes:

[20] - ITT population

[21] - ITT population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Followup period (Week 8 after Open label Phase)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Fulranumab

Reporting group description:

Subjects received Fulranumab [9 milligram (mg) in 0.9 millilitre (mL)] SC once on Day 1 in Double-blind treatment phase. If continued to enter open label phase after double-blind phase, subjects received single SC doses of Fulranumab (9 mg in 0.9 mL) SC once every 4 weeks for a maximum of 12 doses.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo subcutaneous (SC) injection once on Day 1 in Double-blind treatment phase.

Serious adverse events	Fulranumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 67 (88.06%)	22 / 31 (70.97%)	
number of deaths (all causes)	45	18	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant Neoplasm Progression			
subjects affected / exposed	32 / 67 (47.76%)	15 / 31 (48.39%)	
occurrences causally related to treatment / all	0 / 32	0 / 16	
deaths causally related to treatment / all	0 / 31	0 / 15	
Metastases to Bone			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic Neoplasm			

subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal Carcinoma			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Plasma Cell Leukaemia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma Cell Myeloma			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal Cancer			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cancer			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sarcoma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour Haemorrhage			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Circulatory Collapse			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemodynamic Instability			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis Ischaemic			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multi-Organ Failure			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 67 (2.99%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile Oedema			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypercapnia			

subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory Acidosis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			

subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major Depression			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Status Changes			
subjects affected / exposed	4 / 67 (5.97%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional Hernia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Congenital, familial and genetic disorders			

Tracheo-Oesophageal Fistula			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Flutter			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary Failure			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral Ischaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of Consciousness			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neurological Decompensation			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraparesis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 67 (2.99%)	3 / 31 (9.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of Malignant Disease			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphagia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous Fistula			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal Incontinence			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frequent Bowel Movements			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Gastrointestinal Perforation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal Fistula			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth Haemorrhage			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 67 (4.48%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
subjects affected / exposed	4 / 67 (5.97%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary Retention			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			

subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological Fracture			
subjects affected / exposed	1 / 67 (1.49%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lobar Pneumonia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Dehydration			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 67 (2.99%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Fulranumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 67 (88.06%)	28 / 31 (90.32%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	
occurrences (all)	7	4	
Malignant Neoplasm Progression			
subjects affected / exposed	7 / 67 (10.45%)	1 / 31 (3.23%)	
occurrences (all)	7	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 67 (7.46%)	0 / 31 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	18 / 67 (26.87%)	9 / 31 (29.03%)	
occurrences (all)	21	13	
Fatigue			
subjects affected / exposed	8 / 67 (11.94%)	3 / 31 (9.68%)	
occurrences (all)	8	3	
Injection Site Erythema			
subjects affected / exposed	4 / 67 (5.97%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Mucosal Dryness			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Oedema			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Oedema Peripheral			
subjects affected / exposed	16 / 67 (23.88%)	7 / 31 (22.58%)	
occurrences (all)	24	13	
Pain			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	3	
Peripheral Swelling			
subjects affected / exposed	3 / 67 (4.48%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Pyrexia			
subjects affected / exposed	13 / 67 (19.40%)	6 / 31 (19.35%)	
occurrences (all)	21	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 67 (5.97%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Rales			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	
occurrences (all)	1	3	
Dyspnoea			

subjects affected / exposed	9 / 67 (13.43%)	8 / 31 (25.81%)	
occurrences (all)	9	11	
Respiratory Disorder			
subjects affected / exposed	2 / 67 (2.99%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Psychiatric disorders			
Agitation			
subjects affected / exposed	5 / 67 (7.46%)	1 / 31 (3.23%)	
occurrences (all)	6	1	
Anxiety			
subjects affected / exposed	8 / 67 (11.94%)	3 / 31 (9.68%)	
occurrences (all)	10	4	
Confusional State			
subjects affected / exposed	6 / 67 (8.96%)	5 / 31 (16.13%)	
occurrences (all)	6	6	
Hallucination			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Insomnia			
subjects affected / exposed	4 / 67 (5.97%)	4 / 31 (12.90%)	
occurrences (all)	4	5	
Restlessness			
subjects affected / exposed	4 / 67 (5.97%)	3 / 31 (9.68%)	
occurrences (all)	5	3	
Investigations			
Blood Calcium Increased			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Respiratory Rate Decreased			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Fall			

subjects affected / exposed	3 / 67 (4.48%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Fractured Sacrum			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Thermal Burn			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 67 (2.99%)	2 / 31 (6.45%)	
occurrences (all)	4	3	
Nervous system disorders			
Balance Disorder			
subjects affected / exposed	2 / 67 (2.99%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	3 / 67 (4.48%)	5 / 31 (16.13%)	
occurrences (all)	4	7	
Lethargy			
subjects affected / exposed	2 / 67 (2.99%)	3 / 31 (9.68%)	
occurrences (all)	2	3	
Myoclonus			
subjects affected / exposed	6 / 67 (8.96%)	0 / 31 (0.00%)	
occurrences (all)	6	0	
Neuropathy Peripheral			
subjects affected / exposed	0 / 67 (0.00%)	4 / 31 (12.90%)	
occurrences (all)	0	4	
Paraesthesia			
subjects affected / exposed	5 / 67 (7.46%)	5 / 31 (16.13%)	
occurrences (all)	5	7	
Sensory Disturbance			

subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	
occurrences (all)	1	3	
Somnolence			
subjects affected / exposed	5 / 67 (7.46%)	5 / 31 (16.13%)	
occurrences (all)	6	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 67 (16.42%)	3 / 31 (9.68%)	
occurrences (all)	14	3	
Eye disorders			
Eyelid Oedema			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Vision Blurred			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	6 / 67 (8.96%)	4 / 31 (12.90%)	
occurrences (all)	7	6	
Abdominal Pain Lower			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	7 / 67 (10.45%)	3 / 31 (9.68%)	
occurrences (all)	7	3	
Diarrhoea			
subjects affected / exposed	8 / 67 (11.94%)	1 / 31 (3.23%)	
occurrences (all)	8	1	
Dry Mouth			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Dysphagia			
subjects affected / exposed	3 / 67 (4.48%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Nausea			

subjects affected / exposed	17 / 67 (25.37%)	5 / 31 (16.13%)	
occurrences (all)	20	5	
Vomiting			
subjects affected / exposed	12 / 67 (17.91%)	6 / 31 (19.35%)	
occurrences (all)	21	12	
Skin and subcutaneous tissue disorders			
Decubitus Ulcer			
subjects affected / exposed	8 / 67 (11.94%)	3 / 31 (9.68%)	
occurrences (all)	10	10	
Erythema			
subjects affected / exposed	2 / 67 (2.99%)	2 / 31 (6.45%)	
occurrences (all)	4	3	
Hyperhidrosis			
subjects affected / exposed	4 / 67 (5.97%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Pruritus			
subjects affected / exposed	4 / 67 (5.97%)	1 / 31 (3.23%)	
occurrences (all)	5	1	
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Urinary Incontinence			
subjects affected / exposed	2 / 67 (2.99%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Urinary Retention			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 67 (1.49%)	5 / 31 (16.13%)	
occurrences (all)	1	7	
Back Pain			
subjects affected / exposed	4 / 67 (5.97%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Groin Pain			

subjects affected / exposed	0 / 67 (0.00%)	3 / 31 (9.68%)	
occurrences (all)	0	3	
Muscle Spasms			
subjects affected / exposed	4 / 67 (5.97%)	3 / 31 (9.68%)	
occurrences (all)	4	3	
Muscular Weakness			
subjects affected / exposed	6 / 67 (8.96%)	1 / 31 (3.23%)	
occurrences (all)	7	1	
Pathological Fracture			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Infections and infestations			
Candida Infection			
subjects affected / exposed	1 / 67 (1.49%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Pneumonia			
subjects affected / exposed	3 / 67 (4.48%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Sputum Purulent			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 67 (1.49%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Urinary Tract Infection			
subjects affected / exposed	9 / 67 (13.43%)	1 / 31 (3.23%)	
occurrences (all)	13	1	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 67 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Decreased Appetite			
subjects affected / exposed	13 / 67 (19.40%)	4 / 31 (12.90%)	
occurrences (all)	13	6	
Dehydration			

subjects affected / exposed	8 / 67 (11.94%)	2 / 31 (6.45%)	
occurrences (all)	16	2	
Hypercalcaemia			
subjects affected / exposed	2 / 67 (2.99%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Hypokalaemia			
subjects affected / exposed	5 / 67 (7.46%)	2 / 31 (6.45%)	
occurrences (all)	6	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2010	Amendment was made to reduce the number of clinic visits, to limit the number and type of assessments, and add clarifications on some of the prohibitions and restrictions based on feedback from the Investigators. These included: Pharmacogenomic consent, testing, and analysis was eliminated to reduce the visit time and total blood volume based on feedback from the Investigators. The number of clinic visits and assessments were reduced to reduce burden on subjects. Inclusion criteria and prohibitions and restrictions were clarified that subjects cannot donate blood or sperm from screening to 6 months after the last study drug injection. Exclusion criteria was added: Subjects enrolled in an investigational study for an analgesic need to be washed out for 4 weeks, not 8 weeks, or 5 half lives, whichever was longer.
07 April 2010	Amendment allowed subjects at some European sites the option to use a paper diary in place of an e-diary for daily numerical rating scale (NRS) pain and opioid breakthrough pain medication entries. Subjects were to stay on the same type of diary throughout the course of the study. Site staff personnel were to transcribe data from paper diary to an electronic format approved by the sponsor.
18 June 2010	Amendment was made to correct inconsistent statement at the request of an Institutional Review Board (IRB). The following text from safety evaluations, informed consent and privacy of personal data was removed because the inclusion criteria did not allow for subjects who could not make decisions on the own: "or a legally acceptable representative". Also, the following text from Attachment 9 for Weeks 5 and 6 telephone visits was removed: "Please indicate the approximate time and dose amount of each dose of opioid breakthrough pain medication each time a dose is taken."
23 June 2010	Amendment was made to incorporate the changes of Amendment dated on 18-Jun-2010 into the protocol being used at European sites.
25 May 2011	After clinical hold, the targeted population was changed to terminally ill cancer subjects as per the judgment of the investigator (example, subjects who were in or who were candidates for hospice/palliative care for end-of-life management). Prior to the clinical hold, the study enrolled cancer pain subjects on stable doses of baseline around-the-clock opioids (not including breakthrough medication doses) with a life expectancy of greater than 3 months. Based on the debilitated condition of subjects in the target population (that is, terminally ill subjects with cancer-related pain), the number of assessments and blood samples were reduced, the requirements for the injection-site evaluation performed by the subject and the Total Neuropathy Score-Nurse (TNSn) and Mini Mental State Examination (MMSE) performed before administration of each dose of study drug were deleted, the collection of pain assessment scores was simplified (by using paper diaries instead of electronic diaries) and allowing trained caregivers to assist subjects in completing the diaries, and flexibility was added for some safety assessments to reduce the burden to the subjects. The stopping rules for the study and the characterization of hepatic failure and acute renal failure as events of interest were revised. The inclusion and exclusion criteria, and prohibitions and restrictions were modified to reflect common therapies used and comorbidities observed in the terminally ill population. The requirement for a urine pregnancy test was deleted because pregnancy was unlikely to be a risk in this terminally-ill population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported