



## Clinical trial results:

**A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to investigate the efficacy and safety of different intra-articular (i.a.) dosages of sprifermin in subjects with primary osteoarthritis of the knee (FORWARD)**

### Summary

EudraCT number	2011-003059-20
Trial protocol	CZ EE DK PL
Global end of trial date	07 May 2019

### Results information

Result version number	v1 (current)
This version publication date	09 May 2020
First version publication date	09 May 2020

### Trial information

#### Trial identification

Sponsor protocol code	EMR700692_006
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01919164
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Merck KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.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	07 May 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 May 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate structural changes in cartilage thickness in the total femorotibial joint of the target knee in terms of imaging by Magnetic resonance imaging (MRI).

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 2013
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	Estonia: 72
Country: Number of subjects enrolled	Czech Republic: 170
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 61
Country: Number of subjects enrolled	Denmark: 125
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Hong Kong: 108
Worldwide total number of subjects	549
EEA total number of subjects	429

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)	250
From 65 to 84 years	299
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Overall 1366 subjects were screened in this study. Out of which 549 subjects were randomized and received the study treatment into the study.

### 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
<b>Arm title</b>	Placebo

Arm description:

Subjects received Placebo matched to Sprifermin as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received Placebo matched to Sprifermin as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

<b>Arm title</b>	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles
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Arm description:

Subjects received Sprifermin 30 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3; and received placebo matched to Sprifermin once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 26, 27, 28 in Cycle 2 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Arm type	Active comparator
Investigational medicinal product name	AS902330
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarterial use

Dosage and administration details:

Subjects received Sprifermin 30 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3.

<b>Arm title</b>	Sprifermin (AS902330) 30 mcg- 4 Cycles
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Arm description:

Subjects received Sprifermin 30 micrograms (mcg) as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Arm type	Active comparator
Investigational medicinal product name	AS902330
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received Sprifermin 30 micrograms (mcg) as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

<b>Arm title</b>	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
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Arm description:

Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3; and received placebo matched to Sprifermin once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 26, 27, 28 in Cycle 2 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Arm type	Active comparator
Investigational medicinal product name	AS902330
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3.

<b>Arm title</b>	Sprifermin (AS902330) 100 mcg- 4 Cycles
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Arm description:

Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Arm type	Active comparator
Investigational medicinal product name	AS902330
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Number of subjects in period 1	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles
	Started	108	110
Completed	65	80	74
Not completed	43	30	37
Consent withdrawn by subject	13	13	14
Disease progression	2	2	1
Adverse event, non-fatal	6	4	9

Other Un-specified	13	9	8
Death	1	-	-
Lost to follow-up	2	2	2
Protocol deviation	6	-	3

<b>Number of subjects in period 1</b>	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)	Sprifermin (AS902330) 100 mcg- 4 Cycles
	Started	110
Completed	82	77
Not completed	28	33
Consent withdrawn by subject	14	9
Disease progression	2	1
Adverse event, non-fatal	3	2
Other Un-specified	7	15
Death	-	-
Lost to follow-up	-	4
Protocol deviation	2	2

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received Placebo matched to Sprifermin as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	
Reporting group title	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles
Reporting group description: Subjects received Sprifermin 30 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3; and received placebo matched to Sprifermin once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 26, 27, 28 in Cycle 2 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	
Reporting group title	Sprifermin (AS902330) 30 mcg- 4 Cycles
Reporting group description: Subjects received Sprifermin 30 micrograms (mcg) as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	
Reporting group title	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Reporting group description: Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3; and received placebo matched to Sprifermin once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 26, 27, 28 in Cycle 2 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	
Reporting group title	Sprifermin (AS902330) 100 mcg- 4 Cycles
Reporting group description: Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	

Reporting group values	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles
Number of subjects	108	110	111
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	54	46	52
>=65 years	54	64	59
Sex: Female, Male Units: Participants			
Female	76	73	80
Male	32	37	31
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	107	109	111
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0

Asian	21	22	23
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	87	88	88
More than one race	0	0	0
Unknown or Not Reported	0	0	0

<b>Reporting group values</b>	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)	Sprifermin (AS902330) 100 mcg- 4 Cycles	Total
Number of subjects	110	110	549
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	52	46	250
>=65 years	58	64	299
Sex: Female, Male Units: Participants			
Female	77	73	379
Male	33	37	170
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	2
Not Hispanic or Latino	110	110	547
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	21	23	110
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	89	87	439
More than one race	0	0	0
Unknown or Not Reported	0	0	0

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received Placebo matched to Sprifermin as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	
Reporting group title	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles
Reporting group description: Subjects received Sprifermin 30 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3; and received placebo matched to Sprifermin once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 26, 27, 28 in Cycle 2 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	
Reporting group title	Sprifermin (AS902330) 30 mcg- 4 Cycles
Reporting group description: Subjects received Sprifermin 30 micrograms (mcg) as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	
Reporting group title	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Reporting group description: Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3; and received placebo matched to Sprifermin once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 26, 27, 28 in Cycle 2 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	
Reporting group title	Sprifermin (AS902330) 100 mcg- 4 Cycles
Reporting group description: Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.	

### Primary: Change from Baseline in Cartilage Thickness in the Total Femorotibial Joint as Evaluated by Quantitative Magnetic Resonance Imaging (qMRI) at Year 2

End point title	Change from Baseline in Cartilage Thickness in the Total Femorotibial Joint as Evaluated by Quantitative Magnetic Resonance Imaging (qMRI) at Year 2
End point description: The change in cartilage thickness at 2 years was calculated based on quantitative magnetic resonance imaging (qMRI). Modified intent to treat (ITT) analysis set included all randomized subjects that is, only planned treatment regimen was used and who had a baseline, at least 1 post-treatment qMRI assessment available in double-blind placebo-controlled part. Here "Number of subjects analyzed" = subjects evaluable for this endpoint.	
End point type	Primary
End point timeframe: Baseline, Year 2 (Week 104)	

<b>End point values</b>	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	92	83	90
Units: millimeters				
arithmetic mean (standard deviation)	-0.02 (± 0.07)	-0.01 (± 0.07)	0.00 (± 0.07)	0.02 (± 0.08)

<b>End point values</b>	Sprifermin (AS902330) 100 mcg- 4 Cycles			
Subject group type	Reporting group			
Number of subjects analysed	86			
Units: millimeters				
arithmetic mean (standard deviation)	0.03 (± 0.07)			

### Statistical analyses

<b>Statistical analysis title</b>	Placebo vs Sprifermin 30 mcg/placebo - 2 Cycles
Statistical analysis description: Descriptive statistics was provided for primary endpoint.	
Comparison groups	Placebo v Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.03

<b>Statistical analysis title</b>	Placebo vs Sprifermin 30 mcg- 4 Cycles
Statistical analysis description: Descriptive statistics was provided for primary endpoint.	
Comparison groups	Placebo v Sprifermin (AS902330) 30 mcg- 4 Cycles

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.04

<b>Statistical analysis title</b>	Placebo vs Sprifermin 100 mcg/Placebo (2 cycles)
Statistical analysis description: Descriptive statistics was provided for primary endpoint.	
Comparison groups	Placebo v Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.06

<b>Statistical analysis title</b>	Placebo vs Sprifermin 100 mcg- 4 Cycles
Statistical analysis description: Descriptive statistics was provided for primary endpoint.	
Comparison groups	Placebo v Sprifermin (AS902330) 100 mcg- 4 Cycles
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.07

**Secondary: Changes from Baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, Function, Stiffness Index and Total Scores at Week 52, 78 and 104**

End point title	Changes from Baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, Function, Stiffness Index and Total Scores at Week 52, 78 and 104
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End point description:

WOMAC pain subscale consists of 5 questions (Likert Scale) relating to pain. Sum of items of pain subscale ranges from 0-11. Higher scores=worse pain. Stiffness subscale consists of 2 questions relating articular function. Sum of items of stiffness subscale ranges from 0-8. Higher scores=worse function. Physical function subscale consists of 1 question relating to physical activities. Sum of items of physical function subscale ranges from 0-68. Higher scores= worse functional limitations. Each sub-scale is directly transformed into a 0-100 scale, therefore WOMAC total score(24questions) is sum of subscale & ranges from0-100. Higher scores=worse condition. Negative value in change is indicative of improvement. "Number of subjects analyzed" = subjects evaluable for this endpoint & "n" included who were evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline, Week 52, Week 78 and Week 104

End point values	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94	98	89	98
Units: score on a scale				
arithmetic mean (standard deviation)				
Total:Change at Week 52 (n=94,98,87,98,100)	-16.42 (± 18.61)	-17.97 (± 16.95)	-12.64 (± 17.42)	-16.29 (± 18.35)
Total:Change at Week 78 (n=90,94,86,94,94)	-18.41 (± 20.43)	-19.34 (± 19.15)	-16.36 (± 20.35)	-18.88 (± 18.15)
Total:Change at Week 104 (n=86,98,89,96,95)	-22.02 (± 19.70)	-20.73 (± 20.22)	-19.44 (± 20.88)	-18.37 (± 18.69)
Pain: Change at Week 52 (n=94,98,87,98,100)	-18.51 (± 19.49)	-21.55 (± 18.36)	-15.40 (± 18.31)	-21.12 (± 19.73)
Pain: Change at Week 78(n=90,94,86,94,94)	-21.04 (± 20.81)	-23.00 (± 20.42)	-18.19 (± 21.15)	-23.21 (± 19.42)
Pain: Change at Week 104(n=86,98,89,96,95)	-25.37 (± 20.60)	-23.22 (± 21.42)	-21.42 (± 21.37)	-23.15 (± 18.18)
Stiffness: Change at Week 52(n=94,98,87,98,100)	-18.88 (± 24.72)	-18.52 (± 22.89)	-11.09 (± 21.14)	-16.68 (± 20.93)
Stiffness: Change at Week 78(n=90,98,86,94,94)	-20.44 (± 26.76)	-19.47 (± 25.87)	-14.94 (± 23.66)	-19.63 (± 20.38)
Stiffness: Change at Week 104(n=86,98,89,96,95)	-23.20 (± 25.84)	-20.56 (± 23.93)	-17.75 (± 22.74)	-17.76 (± 20.75)
Function: Change at Week 52(n=94,98,87,98,100)	-15.51 (± 19.14)	-16.84 (± 17.64)	-12.01 (± 18.04)	-14.80 (± 19.07)
Function: Change at Week 78(n=90,98,86,94,94)	-17.38 (± 21.01)	-18.23 (± 19.41)	-16.00 (± 20.82)	-17.51 (± 18.96)
Function: Change at Week 104(n=86,98,89,96,95)	-20.89 (± 20.10)	-20.00 (± 20.99)	-19.06 (± 21.52)	-17.03 (± 20.16)

End point values	Sprifermin (AS902330) 100 mcg- 4 Cycles			
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Subject group type	Reporting group			
Number of subjects analysed	100			
Units: score on a scale				
arithmetic mean (standard deviation)				
Total:Change at Week 52 (n=94,98,87,98,100)	-18.29 (± 18.25)			
Total:Change at Week 78 (n=90,94,86,94,94)	-20.29 (± 18.49)			
Total:Change at Week 104 (n=86,98,89,96,95)	-22.08 (± 19.11)			
Pain: Change at Week 52 (n=94,98,87,98,100)	-23.34 (± 17.92)			
Pain: Change at Week 78 (n=90,94,86,94,94)	-23.23 (± 18.41)			
Pain: Change at Week 104 (n=86,98,89,96,95)	-26.06 (± 18.39)			
Stiffness: Change at Week 52 (n=94,98,87,98,100)	-17.35 (± 22.16)			
Stiffness: Change at Week 78 (n=90,98,86,94,94)	-21.44 (± 23.99)			
Stiffness: Change at Week 104 (n=86,98,89,96,95)	-22.79 (± 23.99)			
Function: Change at Week 52 (n=94,98,87,98,100)	-16.91 (± 19.69)			
Function: Change at Week 78 (n=90,98,86,94,94)	-19.29 (± 19.56)			
Function: Change at Week 104 (n=86,98,89,96,95)	-20.82 (± 20.39)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the 20-meter Walk Test at Week 12, 26, 38, 52, 64, 78, 90 and 104

End point title	Change from Baseline in the 20-meter Walk Test at Week 12, 26, 38, 52, 64, 78, 90 and 104
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End point description:

The 20-meter walk test is an objective test of physical function which consists of measuring the time needed for the subject to walk 20 meters at a normal pace. A stopwatch was used for time measurement. Intention-to-Treat (ITT) analysis set included all subjects randomly allocated to a treatment, based on the intention to treat "as randomized" principle. Here "Number of subjects analyzed" = subjects evaluable for this outcome measure and "n" included those who were evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline, Week 12, 26, 38, 52, 64, 78, 90 and 104

<b>End point values</b>	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	108	109	107
Units: seconds				
arithmetic mean (standard deviation)				
Change at Week 12 (n=105,108,109,107,108)	-1.2 (± 2.9)	-0.4 (± 4.0)	-0.5 (± 2.6)	-0.8 (± 2.2)
Change at Week 26 (n=99,108,101,103,102)	-1.3 (± 3.7)	-0.4 (± 3.9)	-0.3 (± 2.6)	-1.1 (± 2.8)
Change at Week 38 (n=98,103,98,102,98)	-1.1 (± 3.6)	-0.5 (± 3.4)	-0.7 (± 2.5)	-1.0 (± 2.9)
Change at Week 52 (n=95,101,90,101,100)	-1.7 (± 4.2)	-1.1 (± 3.6)	-0.7 (± 2.5)	-0.4 (± 7.9)
Change at Week 64 (n=92,101,93,97,93)	-1.8 (± 3.6)	-1.5 (± 4.1)	-0.9 (± 2.5)	-1.3 (± 2.6)
Change at Week 78 (n=91,96,88,97,94)	-1.6 (± 3.7)	-1.0 (± 4.0)	-0.8 (± 2.8)	-1.6 (± 3.0)
Change at Week 90 (n=83,96,87,91,87)	-2.1 (± 3.9)	-1.0 (± 3.2)	-1.1 (± 2.7)	-1.8 (± 3.1)
Change at Week 104 (n=87,100,91,99,94)	-1.6 (± 4.0)	-1.2 (± 4.1)	-0.8 (± 3.4)	-1.4 (± 2.9)

<b>End point values</b>	Sprifermin (AS902330) 100 mcg- 4 Cycles			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: seconds				
arithmetic mean (standard deviation)				
Change at Week 12 (n=105,108,109,107,108)	-1.1 (± 3.3)			
Change at Week 26 (n=99,108,101,103,102)	-1.3 (± 3.0)			
Change at Week 38 (n=98,103,98,102,98)	-1.4 (± 3.2)			
Change at Week 52 (n=95,101,90,101,100)	-1.3 (± 2.8)			
Change at Week 64 (n=92,101,93,97,93)	-1.6 (± 3.4)			
Change at Week 78 (n=91,96,88,97,94)	-1.3 (± 3.2)			
Change at Week 90 (n=83,96,87,91,87)	-1.7 (± 3.5)			
Change at Week 104 (n=87,100,91,99,94)	-1.3 (± 3.2)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Patient's Global Assessment (PGA) at Week 12, 26, 38, 52, 64, 78, 90 and 104

End point title	Change from Baseline in the Patient's Global Assessment (PGA) at Week 12, 26, 38, 52, 64, 78, 90 and 104
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End point description:

The Patient Global Assessment is based on subject's answer to the question "Considering all the ways your osteoarthritis of the knee has affected you during the last 48 Hours, select the number that best describes the impact of your knee osteoarthritis on your daily life", and can take on values between 0-10 (0=None, 10=Extreme), for summaries the values are rescaled to 0-100 by multiplication with 10. Higher scores indicated worsening of condition. A negative value in change in Patient's Global Assessment is indicative of an improvement. Intention-to-Treat (ITT) analysis set included all subjects randomly allocated to a treatment, based on the intention to treat "as randomized" principle. Here "Number of subjects analyzed" = subjects evaluable for this outcome measure and "n" included those who were evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline, Week 12, 26, 38, 52, 64, 78, 90 and 104

End point values	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	108	109	106
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n=104,108,109,106,107)	-16.6 (± 23.5)	-13.9 (± 20.6)	-17.0 (± 25.0)	-15.0 (± 23.2)
Change at Week 26 (n=99,108,100,103,102)	-16.3 (± 22.3)	-15.1 (± 22.7)	-17.7 (± 25.3)	-18.7 (± 22.4)
Change at Week 38 (n=98,103,97,102,98)	-18.9 (± 26.2)	-17.2 (± 22.5)	-19.2 (± 24.9)	-20.5 (± 24.3)
Change at Week 52 (n=95,100,88,101,100)	-19.6 (± 25.8)	-20.9 (± 21.2)	-18.0 (± 23.9)	-19.5 (± 25.2)
Change at Week 64 (n=92,101,93,97,93)	-22.7 (± 24.6)	-21.7 (± 21.9)	-22.3 (± 23.0)	-21.6 (± 25.8)
Change at Week 78 (n=91,96,88,97,93)	-22.7 (± 26.5)	-21.5 (± 24.1)	-23.1 (± 25.7)	-22.0 (± 25.4)
Change at Week 90 (n=83,97,87,91,87)	-25.8 (± 25.6)	-22.3 (± 24.5)	-21.7 (± 24.8)	-21.1 (± 26.3)
Change at Week 104 (n=87,100,91,99,95)	-27.5 (± 25.0)	-23.0 (± 22.3)	-23.8 (± 24.9)	-22.1 (± 25.6)

End point values	Sprifermin (AS902330) 100 mcg- 4 Cycles			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 12 (n=104,108,109,106,107)	-16.7 (± 22.1)			
Change at Week 26 (n=99,108,100,103,102)	-19.1 (± 24.1)			
Change at Week 38 (n=98,103,97,102,98)	-18.4 (± 25.1)			

Change at Week 52 (n=95,100,88,101,100)	-21.6 (± 24.0)			
Change at Week 64 (n=92,101,93,97,93)	-21.3 (± 24.6)			
Change at Week 78 (n=91,96,88,97,93)	-24.2 (± 24.1)			
Change at Week 90 (n=83,97,87,91,87)	-26.2 (± 24.9)			
Change at Week 104 (n=87,100,91,99,95)	-25.8 (± 22.8)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Minimal Joint Space Width (mJSW) in the Medial and Lateral Compartments as Evaluated by X-ray at Week 52 and 104

End point title	Change from Baseline in Minimal Joint Space Width (mJSW) in the Medial and Lateral Compartments as Evaluated by X-ray at Week 52 and 104
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End point description:

Change in joint space narrowing was visualized with the "fixed flexion" knee radiograph. Determination of joint space narrowing by X-ray is considered to be a semi-quantitative method for assessment of progression of knee osteoarthritis (OA). X-rays of both the target knee and the contralateral knee were performed. X-rays were read centrally. X-ray images were used to measure mJSW in the medial femorotibial and lateral femorotibial compartments and to determine the subject's baseline Kellgren-Lawrence grades (KLG). Intention-to-Treat (ITT) analysis set included all subjects randomly allocated to a treatment, based on the intention to treat "as randomized" principle. Here "Number of subjects analyzed" = subjects evaluable for this outcome measure and "n" included those who were evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline, Week 52 and 104

End point values	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	95	101	95	100
Units: millimeter				
arithmetic mean (standard deviation)				
Medial: at Week 52 (n=95,97,89,100,101)	-0.10 (± 0.48)	-0.05 (± 0.53)	-0.04 (± 0.43)	0.02 (± 0.55)
Medial: at Week 104 (n=90,101,95,98,95)	-0.11 (± 0.59)	-0.09 (± 0.73)	0.03 (± 0.52)	-0.05 (± 0.66)
Lateral: at Week 52 (n=95,97,89,100,101)	0.07 (± 0.46)	-0.03 (± 0.62)	0.16 (± 0.54)	0.10 (± 0.37)
Lateral: at Week 104 (n=90,101,95,98,95)	-0.07 (± 0.49)	-0.03 (± 0.64)	0.01 (± 0.65)	0.19 (± 0.49)

<b>End point values</b>	Sprifermin (AS902330) 100 mcg- 4 Cycles			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: millimeter				
arithmetic mean (standard deviation)				
Medial: at Week 52 (n=95,97,89,100,101)	-0.04 (± 0.57)			
Medial: at Week 104 (n=90,101,95,98,95)	-0.07 (± 0.86)			
Lateral: at Week 52 (n=95,97,89,100,101)	0.14 (± 0.43)			
Lateral: at Week 104 (n=90,101,95,98,95)	0.19 (± 0.49)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Cartilage Thickness in the Medial and Lateral Compartments as well as in the Total Femorotibial Joint at 26, 52, 78 and 104

End point title	Change from Baseline in Cartilage Thickness in the Medial and Lateral Compartments as well as in the Total Femorotibial Joint at 26, 52, 78 and 104
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End point description:

The change in cartilage thickness at Week 26, 52, 78 and 104 was calculated based on quantitative magnetic resonance imaging (qMRI). Modified intent to treat (ITT) analysis set included all randomized subjects that is, only planned treatment regimen was used and who had a baseline, at least 1 post-treatment qMRI assessment available in double-blind placebo-controlled part. Here "Number of subjects analyzed" = subjects evaluable for this outcome measure and "n" included those who were evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline, Week 26, 52, 78 and 104

<b>End point values</b>	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94	97	97	96
Units: millimeter				
arithmetic mean (standard deviation)				
Medial: at Week 26 (n=93,97,95,95,99)	0.00 (± 0.06)	0.00 (± 0.06)	-0.01 (± 0.06)	0.01 (± 0.05)
Medial: at Week 52 (n=91,93,81,94,93)	-0.01 (± 0.06)	-0.01 (± 0.07)	-0.01 (± 0.06)	0.00 (± 0.07)
Medial: at Week 78 (n=84,91,84,90,89)	-0.01 (± 0.07)	-0.01 (± 0.07)	0.01 (± 0.06)	0.01 (± 0.10)
Medial: at Week 104 (n=83,92,83,90,86)	-0.03 (± 0.12)	-0.02 (± 0.10)	-0.01 (± 0.08)	0.00 (± 0.11)
Lateral: at Week 26 (n=94,97,97,96,99)	-0.01 (± 0.05)	0.00 (± 0.05)	0.00 (± 0.06)	0.02 (± 0.05)

Lateral: at Week 52 (n=92,93,83,95,93)	-0.01 (± 0.05)	-0.01 (± 0.07)	0.00 (± 0.05)	0.02 (± 0.06)
Lateral: at Week 78 (n=85,91,85,91,89)	0.00 (± 0.05)	0.01 (± 0.06)	0.01 (± 0.08)	0.03 (± 0.07)
Lateral: at Week 104 (n=83,92,85,91,86)	-0.01 (± 0.05)	-0.01 (± 0.07)	0.00 (± 0.09)	0.04 (± 0.07)
Total: at Week 26 (n=93,97,95,95,99)	-0.01 (± 0.05)	0.00 (± 0.04)	0.00 (± 0.05)	0.01 (± 0.04)
Total: at Week 52 (n=91,93,81,94,93)	-0.01 (± 0.05)	-0.01 (± 0.06)	0.00 (± 0.05)	0.01 (± 0.06)
Total: Change at Week 78 (n=84,91,84,90,89)	-0.01 (± 0.05)	0.00 (± 0.06)	0.06 (± 0.06)	0.02 (± 0.07)
Total: Change at Week 104 (n=83,92,83,96,86)	-0.02 (± 0.07)	-0.01 (± 0.07)	0.00 (± 0.07)	0.02 (± 0.08)

<b>End point values</b>	Sprifermin (AS902330) 100 mcg- 4 Cycles			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: millimeter				
arithmetic mean (standard deviation)				
Medial: at Week 26 (n=93,97,95,95,99)	0.01 (± 0.06)			
Medial: at Week 52 (n=91,93,81,94,93)	0.01 (± 0.06)			
Medial: at Week 78 (n=84,91,84,90,89)	0.03 (± 0.08)			
Medial: at Week 104 (n=83,92,83,90,86)	0.02 (± 0.08)			
Lateral: at Week 26 (n=94,97,97,96,99)	0.02 (± 0.05)			
Lateral: at Week 52 (n=92,93,83,95,93)	0.02 (± 0.05)			
Lateral: at Week 78 (n=85,91,85,91,89)	0.03 (± 0.06)			
Lateral: at Week 104 (n=83,92,85,91,86)	0.04 (± 0.06)			
Total: at Week 26 (n=93,97,95,95,99)	0.01 (± 0.05)			
Total: at Week 52 (n=91,93,81,94,93)	0.01 (± 0.05)			
Total: Change at Week 78 (n=84,91,84,90,89)	0.03 (± 0.06)			
Total: Change at Week 104 (n=83,92,83,96,86)	0.03 (± 0.07)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Cartilage-Volume in the Medial and Lateral Compartments as well as in the Total Femorotibial Joint at Week 26, 52, 78 and 104

End point title	Change from Baseline in Cartilage-Volume in the Medial and Lateral Compartments as well as in the Total Femorotibial Joint at Week 26, 52, 78 and 104
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End point description:

The change in cartilage volume in the medial and lateral compartments as well as in the total femorotibial joint at Week 26, 52, 78 and 104 was calculated based on qMRI. Modified ITT analysis set was used. Here "Number of subjects analyzed" = subjects evaluable for this outcome measure and "n" included those who were evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Baseline, Week 26, 52, 78 and 104

<b>End point values</b>	Placebo	Sprifermin (AS902330) 30 mcg/Placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	101	98	99
Units: microliter				
arithmetic mean (standard deviation)				
Medial: at Week 26 (n=93,97,95,95,99)	0.0 (± 112.2)	1.7 (± 110.8)	-3.2 (± 99.5)	16.7 (± 89.8)
Medial: at Week 52 (n=91,93,81,94,93)	-10.2 (± 100.7)	-2.9 (± 127.1)	-7.0 (± 103.7)	3.6 (± 127.5)
Medial: at Week 78 (n=84,91,84,90,89)	-8.9 (± 125.3)	-7.0 (± 153.7)	23.6 (± 109.3)	33.2 (± 177.0)
Medial: at Week 104 (n=83,92,83,90,86)	-41.0 (± 192.1)	-21.4 (± 198.3)	3.6 (± 123.9)	19.5 (± 202.3)
Lateral: at Week 26 (n=94,97,97,96,99)	-12.8 (± 84.4)	0.8 (± 82.0)	1.5 (± 102.3)	31.3 (± 87.7)
Lateral: at Week 52 (n=92,93,83,95,93)	-12.7 (± 94.0)	-17.5 (± 141.1)	2.7 (± 98.2)	32.4 (± 107.5)
Lateral: at Week 78 (n=85,91,85,91,89)	-1.8 (± 89.7)	13.9 (± 113.6)	21.6 (± 129.0)	55.9 (± 123.1)
Lateral: at Week 104 (n=83,92,85,91,86)	-14.5 (± 87.2)	-6.8 (± 144.9)	7.2 (± 134.8)	75.5 (± 111.8)
Total: at Week 26 (n=93,97,95,95,99)	-13.0 (± 163.2)	2.5 (± 147.0)	-2.9 (± 161.8)	48.4 (± 150.9)
Total: at Week 52 (n=91,93,81,94,93)	-23.7 (± 155.7)	-20.4 (± 217.6)	-5.5 (± 169.0)	36.2 (± 203.1)
Total: Change at Week 78 (n=84,91,84,90,89)	-10.3 (± 176.8)	6.9 (± 228.1)	44.8 (± 195.3)	89.9 (± 272.6)
Total: Change at Week 104 (n=83,92,83,90,86)	-55.5 (± 239.5)	-28.2 (± 275.7)	9.5 (± 205.7)	96.6 (± 271.1)

<b>End point values</b>	Sprifermin (AS902330) 100 mcg- 4 Cycles			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: microliter				
arithmetic mean (standard deviation)				
Medial: at Week 26 (n=93,97,95,95,99)	16.5 (± 114.2)			
Medial: at Week 52 (n=91,93,81,94,93)	16.5 (± 110.6)			
Medial: at Week 78 (n=84,91,84,90,89)	53.9 (± 147.3)			
Medial: at Week 104 (n=83,92,83,90,86)	48.6 (± 150.7)			
Lateral: at Week 26 (n=94,97,97,96,99)	25.1 (± 85.8)			
Lateral: at Week 52 (n=92,93,83,95,93)	28.1 (± 87.3)			
Lateral: at Week 78 (n=85,91,85,91,89)	55.2 (± 101.6)			
Lateral: at Week 104 (n=83,92,85,91,86)	67.9 (± 112.5)			
Total: at Week 26 (n=93,97,95,95,99)	41.5 (± 166.6)			

Total: at Week 52 (n=91,93,81,94,93)	44.7 (± 163.2)			
Total: Change at Week 78 (n=84,91,84,90,89)	109.1 (± 219.1)			
Total: Change at Week 104 (n=83,92,83,90,86)	116.5 (± 233.5)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Synovial Fluid Levels of sprifermin/FGF-18

End point title	Synovial Fluid Levels of sprifermin/FGF-18
End point description:	Levels of sprifermin/FGF-18 in synovial fluid were measured to provide a first estimate of the residence time of sprifermin in the synovial fluid. Safety analysis set included all subjects who received at least 1 dose of study treatment. Arm assignments for subjects in Safety Set were based on actual treatment received. Here "Number of subjects analyzed" = subjects evaluable for this outcome measure and "n" included those who were evaluable at specified timepoints. "n" also signifies subjects evaluable at specified time points and "99999" signifies "NA".
End point type	Secondary
End point timeframe:	Pre-dose at Week 0 thereafter 2 hours post-dose at Week 1, 2 and 3 of Cycle 1, 2, 3 and 4 (each cycle is of 28 days)

End point values	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	20	22	25
Units: picogram/milliliter				
median (full range (min-max))				
Week 0; Cycle 1 (n=5,5,5,8,0)	99999 (99999 to 99999)	56876.4 (5843.8 to 86068.0)	1006.5 (206.6 to 34439.4)	1386.1 (260.4 to 36766.4)
Week 1; Cycle 1 (n=5,7,10,16,2)	622.1 (156.0 to 1088.2)	3628.3 (229.9 to 37140.5)	1493.2 (214.2 to 110515.4)	359.8 (151.2 to 37014.8)
Week 2; Cycle 1 (n=10,6,12,16,0)	99999 (99999 to 99999)	3150.9 (189.1 to 33378.5)	4167.0 (460.3 to 8857.1)	467.9 (150.7 to 108866.0)
Week 0; Cycle 3 (n=20,15,9,13,3)	463.7 (223.8 to 5386.5)	8019.3 (279.2 to 358231.4)	9443.4 (505.7 to 271320.6)	16901.2 (461.0 to 273247.0)
Week 1; Cycle 3 (n=14,11,16,22,0)	99999 (99999 to 99999)	8607.6 (276.7 to 147723.9)	4605.1 (337.2 to 358029.6)	3908.8 (177.5 to 86823.9)
Week 2; Cycle 3 (n=15,15,25,25,1)	260.9 (260.9 to 260.9)	9592.2 (1277.1 to 35615.5)	9422.2 (409.3 to 353582.4)	1801.0 (171.9 to 77338.9)
Week 0; Cycle 2 (n=0,10,1,13,1)	202.5 (202.5 to 202.5)	99999 (99999 to 99999)	7039.1 (309.8 to 1108182.4)	308.2 (308.2 to 308.2)
Week 1; Cycle 2 (n=0,17,0,16,0)	99999 (99999 to 99999)	99999 (99999 to 99999)	14756.3 (904.6 to 359059.2)	99999 (99999 to 99999)

Week 2; Cycle 2 (n=0,16,0,18,0)	99999 (99999 to 99999)	99999 (99999 to 99999)	6408.3 (154.4 to 220629.5)	99999 (99999 to 99999)
Week 0; Cycle 4 (n=0,17,0,16,0)	99999 (99999 to 99999)	99999 (99999 to 99999)	12458.4 (224.6 to 163129.3)	99999 (99999 to 99999)
Week 1; Cycle 4 (n=0,18,1,22,1)	215.3 (215.3 to 215.3)	99999 (99999 to 99999)	9602.7 (178.6 to 45631.9)	2285.2 (2285.2 to 2285.2)
Week 2; Cycle 4 (n=0,22,2,27,1)	10670.0 (10670.0 to 10670.0)	99999 (99999 to 99999)	7103.8 (196.8 to 384511.5)	331.1 (168.4 to 493.7)

<b>End point values</b>	Sprifermin (AS902330) 100 mcg- 4 Cycles			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: picogram/milliliter				
median (full range (min-max))				
Week 0; Cycle 1 (n=5,5,5,8,0)	5896.4 (631.3 to 238780.1)			
Week 1; Cycle 1 (n=5,7,10,16,2)	1062.3 (156.7 to 840122.2)			
Week 2; Cycle 1 (n=10,6,12,16,0)	258.2 (171.9 to 48066.3)			
Week 0; Cycle 3 (n=20,15,9,13,3)	20753.0 (4119.1 to 303440.5)			
Week 1; Cycle 3 (n=14,11,16,22,0)	10160.0 (165.5 to 375638.7)			
Week 2; Cycle 3 (n=15,15,25,25,1)	4161.7 (151.1 to 213692.3)			
Week 0; Cycle 2 (n=0,10,1,13,1)	32360.2 (559.9 to 683691.9)			
Week 1; Cycle 2 (n=0,17,0,16,0)	7036.9 (159.9 to 82301.6)			
Week 2; Cycle 2 (n=0,16,0,18,0)	1146.7 (156.1 to 42598.5)			
Week 0; Cycle 4 (n=0,17,0,16,0)	22132.1 (215.7 to 897758.2)			
Week 1; Cycle 4 (n=0,18,1,22,1)	11468.3 (157.5 to 142318.7)			
Week 2; Cycle 4 (n=0,22,2,27,1)	8026.4 (179.7 to 272804.6)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Levels of Sprifermin/FGF-18

End point title	Serum Levels of Sprifermin/FGF-18
End point description:	Serum levels of AS902330/FGF-18 could not be analyzed because the serum concentrations were not quantifiable, as serum sprifermin concentrations were below Lower Limit of Quantification (LLOQ). LLOQ=100 picogram/milliliter.
End point type	Secondary
End point timeframe:	Pre-dose at Week 0, 2 hours post-dose at Week 1, 2 and 3 of Cycle 1, 2, 3 and 4 (each cycle is of 28 days)

End point values	Placebo	Sprifermin (AS902330) 30 mcg/placebo - 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[1]</sup>	0 <sup>[2]</sup>	0 <sup>[3]</sup>	0 <sup>[4]</sup>
Units: picogram/milliliter				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

- [1] - Serum levels of AS902330/FGF-18 could not be analyzed.
- [2] - Serum levels of AS902330/FGF-18 could not be analyzed.
- [3] - Serum levels of AS902330/FGF-18 could not be analyzed.
- [4] - Serum levels of AS902330/FGF-18 could not be analyzed.

End point values	Sprifermin (AS902330) 100 mcg- 4 Cycles			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[5]</sup>			
Units: picogram/milliliter				
arithmetic mean (standard deviation)	()			

Notes:

- [5] - Serum levels of AS902330/FGF-18 could not be analyzed.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 5 years

Adverse event reporting additional description:

Adverse events presented as per Safety Set. Assignments for subjects in Safety Set were based on actual drug received, such that 1 subject assigned to Placebo arm who received 30mcg was included in Sprifermin 30mcg-2Cycles arm and 1 subject assigned to Sprifermin 30mcg/placebo-2Cycles arm who received 100mcg was included in Sprifermin 100mcg-2Cycles arm.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received Placebo matched to Sprifermin as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Reporting group title	Sprifermin (AS902330) 30 mcg- 2 Cycles
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Reporting group description:

Subjects received Sprifermin 30 micrograms (mcg) as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3; and received placebo matched to Sprifermin once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 26, 27, 28 in Cycle 2 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Reporting group title	Sprifermin (AS902330) 30 mcg- 4 Cycles
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Reporting group description:

Subjects received Sprifermin 30 micrograms (mcg) as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Reporting group title	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)
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Reporting group description:

Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 0, 1, 2 in Cycle 1 and at week 52, 53, 54 in Cycle 3; and received placebo matched to Sprifermin once every week for 3 consecutive weeks for 2 alternative cycles, that is at week 26, 27, 28 in Cycle 2 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

Reporting group title	Sprifermin (AS902330) 100 mcg- 4 Cycles
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Reporting group description:

Subjects received Sprifermin 100 mcg as intra-articular injection once every week for 3 consecutive weeks for 4 cycles, that is at week 0, 1, 2 in Cycle 1; at week 26, 27, 28 in Cycle 2; at week 52, 53, 54 in Cycle 3 and at week 78, 79, 80 in Cycle 4 at interval of 6 months.

<b>Serious adverse events</b>	Placebo	Sprifermin (AS902330) 30 mcg- 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 107 (36.45%)	35 / 109 (32.11%)	34 / 111 (30.63%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 107 (0.00%)	2 / 109 (1.83%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Benign breast neoplasm			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Benign pancreatic neoplasm			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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

Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Carcinoid tumour			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Carcinoid tumour of the gastrointestinal tract			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Colon cancer metastatic			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Fibroma			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Follicular thyroid cancer			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Gastric cancer			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Metastases to liver			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Metastatic gastric cancer</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Papillary cystadenoma lymphomatosum</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Renal cell carcinoma</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Renal oncocytoma</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Sarcoma</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Uterine leiomyoma</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Vascular disorders</b>			
<b>Hypertension</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Aortic aneurysm</b>			

subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Aortic stenosis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Deep vein thrombosis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Peripheral artery thrombosis</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Thrombosis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Varicose vein</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Surgical and medical procedures</b>			
<b>Removal of internal fixation</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>General disorders and administration site conditions</b>			
<b>Chest pain</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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

Malaise			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Peripheral swelling			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Colpocele			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Uterine polyp			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Uterine prolapse			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Vulvar dysplasia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Pulmonary embolism			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Sleep apnoea syndrome			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Product issues			
Device dislocation			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Injury, poisoning and procedural complications			
Meniscus injury			

subjects affected / exposed	2 / 107 (1.87%)	1 / 109 (0.92%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Contusion</b>			
subjects affected / exposed	2 / 107 (1.87%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Wrist fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	2 / 109 (1.83%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Ankle fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Clavicle fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Concussion</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Facial bones fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Femoral neck fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Foot fracture</b>			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Hand fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Head injury</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Muscle strain</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Pelvic fracture</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Periprosthetic fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Skin injury</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Skin laceration</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Stress fracture</b>			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Subdural haematoma</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Tendon rupture</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Tibia fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Toxicity to various agents</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Upper limb fracture</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Wound dehiscence</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac disorders</b>			
<b>Acute myocardial infarction</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Angina pectoris</b>			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Atrial fibrillation</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Atrial flutter</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Coronary artery stenosis</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Myocardial infarction</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Angina unstable</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	2 / 111 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac failure congestive</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Myocardial ischaemia</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Aortic valve stenosis</b>			

subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Arrhythmia</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Bradycardia</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Cardiac failure</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Cardiomyopathy</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Pericarditis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Stress cardiomyopathy</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Supraventricular extrasystoles</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Ventricular extrasystoles</b>			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Syncope			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arachnoid cyst			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Brain stem infarction			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Carpal tunnel syndrom			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Cerebral ischaemia			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Cubital tunnel syndrome			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Dizziness			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Meningeal disorder			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Trigeminal neuralgia			

subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Blood and lymphatic system disorders</b>			
Iron deficiency anaemia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Ear and labyrinth disorders</b>			
Vertigo			
subjects affected / exposed	1 / 107 (0.93%)	1 / 109 (0.92%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Eye disorders</b>			
Retinal detachment			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Gastrointestinal disorders</b>			
Gastritis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia obstructive			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Colitis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Diverticulum			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Gastric ulcer			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Loose tooth			

subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Pancreatitis acute</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Parotid gland enlargement</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Umbilical hernia</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Hepatobiliary disorders</b>			
<b>Cholecystitis</b>			
subjects affected / exposed	2 / 107 (1.87%)	0 / 109 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cholecystitis acute</b>			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Cholelithiasis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Bile duct stone</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Cholangitis acute</b>			

subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Skin and subcutaneous tissue disorders</b>			
Panniculitis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Renal and urinary disorders</b>			
Urinary retention			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neck obstruction			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Haematuria			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal infarct			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Endocrine disorders</b>			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Toxic nodular goitre			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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	9 / 107 (8.41%)	10 / 109 (9.17%)	7 / 111 (6.31%)
occurrences causally related to treatment / all	0 / 9	0 / 10	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	3 / 107 (2.80%)	2 / 109 (1.83%)	3 / 111 (2.70%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 107 (0.00%)	4 / 109 (3.67%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondropathy			
subjects affected / exposed	2 / 107 (1.87%)	0 / 109 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Arthritis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Dupuytren's contracture			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Foot deformity			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Joint effusion			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Spinal column stenosis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Spondylolisthesis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
Synovitis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Torticollis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
Trigger finger			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
Vertebral foraminal stenosis			

subjects affected / exposed	0 / 107 (0.00%)	1 / 109 (0.92%)	0 / 111 (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
<b>Infections and infestations</b>			
<b>Pneumonia</b>			
subjects affected / exposed	0 / 107 (0.00%)	2 / 109 (1.83%)	4 / 111 (3.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Urinary tract infection</b>			
subjects affected / exposed	1 / 107 (0.93%)	1 / 109 (0.92%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Appendicitis</b>			
subjects affected / exposed	2 / 107 (1.87%)	0 / 109 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bronchitis</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Arthritis bacterial</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cellulitis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cystitis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Diverticulitis</b>			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Erysipelas</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Gastroenteritis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Influenza</b>			
subjects affected / exposed	1 / 107 (0.93%)	0 / 109 (0.00%)	0 / 111 (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
<b>Lower respiratory tract infection</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Otitis media chronic</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Sialoadenitis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Tonsillitis</b>			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Urosepsis</b>			

subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	0 / 111 (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
<b>Metabolism and nutrition disorders</b>			
Dehydration			
subjects affected / exposed	0 / 107 (0.00%)	0 / 109 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)	Sprifermin (AS902330) 100 mcg- 4 Cycles	
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	32 / 111 (28.83%)	41 / 109 (37.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
Colon cancer			
subjects affected / exposed	0 / 111 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Benign breast neoplasm</b>			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Benign pancreatic neoplasm</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Benign salivary gland neoplasm</b>			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bladder transitional cell carcinoma</b>			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Carcinoid tumour</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Carcinoid tumour of the gastrointestinal tract</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Colon cancer metastatic</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Diffuse large B-cell lymphoma</b>			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroma			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Follicular thyroid cancer			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic gastric cancer			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal oncocytoma			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Sarcoma</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Uterine leiomyoma</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vascular disorders</b>			
<b>Hypertension</b>			
subjects affected / exposed	0 / 111 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Aortic aneurysm</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Aortic stenosis</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Deep vein thrombosis</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Peripheral artery thrombosis</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Thrombosis</b>			

subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Removal of internal fixation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (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			
Chest pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	2 / 111 (1.80%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colpocele			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvar dysplasia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (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			
Meniscus injury			
subjects affected / exposed	0 / 111 (0.00%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clavicle fracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 111 (1.80%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 111 (0.90%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 111 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	2 / 111 (1.80%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			

subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 111 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Arachnoid cyst</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Brain stem infarction</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Carpal tunnel syndrom</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cerebral ischaemia</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Chronic inflammatory demyelinating polyradiculoneuropathy</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cubital tunnel syndrome</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Dizziness</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Haemorrhagic stroke</b>			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Meningeal disorder</b>			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Subarachnoid haemorrhage</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Transient ischaemic attack</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Trigeminal neuralgia</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Blood and lymphatic system disorders</b>			
<b>Iron deficiency anaemia</b>			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ear and labyrinth disorders</b>			
<b>Vertigo</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vertigo positional</b>			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Eye disorders</b>			

Retinal detachment			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	2 / 111 (1.80%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia obstructive			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loose tooth			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland enlargement			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cholelithiasis</b>			
subjects affected / exposed	1 / 111 (0.90%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bile duct stone</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cholangitis acute</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Skin and subcutaneous tissue disorders</b>			
<b>Panniculitis</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
<b>Urinary retention</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bladder neck obstruction</b>			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Haematuria</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal infarct</b>			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Endocrine disorders</b>			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic nodular goitre			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Osteoarthritis			
subjects affected / exposed	7 / 111 (6.31%)	7 / 109 (6.42%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 111 (0.00%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondropathy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 111 (0.90%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 111 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torticollis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			

subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			

subjects affected / exposed	1 / 111 (0.90%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Sialoadenitis</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Tonsillitis</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Urosepsis</b>			
subjects affected / exposed	0 / 111 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
<b>Dehydration</b>			
subjects affected / exposed	0 / 111 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	Sprifermin (AS902330) 30 mcg- 2 Cycles	Sprifermin (AS902330) 30 mcg- 4 Cycles
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 107 (98.13%)	106 / 109 (97.25%)	109 / 111 (98.20%)
<b>Vascular disorders</b>			
<b>Hypertension</b>			
subjects affected / exposed	17 / 107 (15.89%)	24 / 109 (22.02%)	14 / 111 (12.61%)
occurrences (all)	17	24	14
<b>General disorders and administration site conditions</b>			
<b>Injection site pain</b>			
subjects affected / exposed	6 / 107 (5.61%)	5 / 109 (4.59%)	10 / 111 (9.01%)
occurrences (all)	6	5	10

Injection site bruising subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4	5 / 109 (4.59%) 5	6 / 111 (5.41%) 6
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	9 / 107 (8.41%) 9	12 / 109 (11.01%) 12	12 / 111 (10.81%) 12
Oropharyngeal pain subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7	1 / 109 (0.92%) 1	1 / 111 (0.90%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	0 / 109 (0.00%) 0	7 / 111 (6.31%) 7
Investigations C-reactive protein increased subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	2 / 109 (1.83%) 2	0 / 111 (0.00%) 0
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	18 / 107 (16.82%) 18	9 / 109 (8.26%) 9	9 / 111 (8.11%) 9
Contusion subjects affected / exposed occurrences (all)	5 / 107 (4.67%) 5	9 / 109 (8.26%) 9	9 / 111 (8.11%) 9
Ligament sprain subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6	5 / 109 (4.59%) 5	6 / 111 (5.41%) 6
Skin abrasion subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	5 / 109 (4.59%) 5	7 / 111 (6.31%) 7
Nervous system disorders Headache subjects affected / exposed occurrences (all)	15 / 107 (14.02%) 15	14 / 109 (12.84%) 14	11 / 111 (9.91%) 11
Sciatica			

subjects affected / exposed occurrences (all)	11 / 107 (10.28%) 11	8 / 109 (7.34%) 8	4 / 111 (3.60%) 4
Dizziness subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7	3 / 109 (2.75%) 3	3 / 111 (2.70%) 3
Hypoaesthesia subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7	4 / 109 (3.67%) 4	5 / 111 (4.50%) 5
Memory impairment subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4	0 / 109 (0.00%) 0	6 / 111 (5.41%) 6
Eye disorders Cataract subjects affected / exposed occurrences (all)	8 / 107 (7.48%) 8	6 / 109 (5.50%) 6	10 / 111 (9.01%) 10
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	6 / 109 (5.50%) 5	3 / 111 (2.70%) 3
Diarrhoea subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	4 / 109 (3.67%) 4	4 / 111 (3.60%) 4
Gastritis subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4	4 / 109 (3.67%) 4	4 / 111 (3.60%) 4
Toothache subjects affected / exposed occurrences (all)	5 / 107 (4.67%) 5	2 / 109 (1.83%) 2	4 / 111 (3.60%) 4
Dyspepsia subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4	7 / 109 (6.42%) 7	2 / 111 (1.80%) 2
Abdominal pain subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	3 / 109 (2.75%) 3	2 / 111 (1.80%) 2
Endocrine disorders			

Hypothyroidism subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	1 / 109 (0.92%) 1	1 / 111 (0.90%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	58 / 107 (54.21%) 58	59 / 109 (54.13%) 59	57 / 111 (51.35%) 57
Back pain subjects affected / exposed occurrences (all)	24 / 107 (22.43%) 24	28 / 109 (25.69%) 28	29 / 111 (26.13%) 29
Osteoarthritis subjects affected / exposed occurrences (all)	21 / 107 (19.63%) 21	22 / 109 (20.18%) 22	24 / 111 (21.62%) 24
Musculoskeletal pain subjects affected / exposed occurrences (all)	20 / 107 (18.69%) 20	16 / 109 (14.68%) 16	18 / 111 (16.22%) 18
Pain in extremity subjects affected / exposed occurrences (all)	15 / 107 (14.02%) 15	12 / 109 (11.01%) 12	24 / 111 (21.62%) 24
Joint swelling subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 10	14 / 109 (12.84%) 14	11 / 111 (9.91%) 11
Neck pain subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7	4 / 109 (3.67%) 4	9 / 111 (8.11%) 9
Spinal pain subjects affected / exposed occurrences (all)	5 / 107 (4.67%) 5	1 / 109 (0.92%) 1	5 / 111 (4.50%) 5
Muscle spasms subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6	4 / 109 (3.67%) 4	4 / 111 (3.60%) 4
Myalgia subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4	4 / 109 (3.67%) 4	8 / 111 (7.21%) 8
Periarthritis			

subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	8 / 109 (7.34%) 8	5 / 111 (4.50%) 5
Plantar fasciitis subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	6 / 109 (5.50%) 6	7 / 111 (6.31%) 7
Tendonitis subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	8 / 109 (7.34%) 8	2 / 111 (1.80%) 2
Arthritis subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2	4 / 109 (3.67%) 4	2 / 111 (1.80%) 2
<b>Infections and infestations</b>			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	21 / 107 (19.63%) 21	25 / 109 (22.94%) 25	28 / 111 (25.23%) 28
Nasopharyngitis subjects affected / exposed occurrences (all)	27 / 107 (25.23%) 27	25 / 109 (22.94%) 25	20 / 111 (18.02%) 20
Urinary tract infection subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 10	13 / 109 (11.93%) 13	10 / 111 (9.01%) 10
Influenza subjects affected / exposed occurrences (all)	13 / 107 (12.15%) 13	10 / 109 (9.17%) 10	11 / 111 (9.91%) 11
Cystitis subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7	15 / 109 (13.76%) 15	8 / 111 (7.21%) 8
Bronchitis subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 10	11 / 109 (10.09%) 11	6 / 111 (5.41%) 6
Pneumonia subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6	9 / 109 (8.26%) 9	7 / 111 (6.31%) 7
Viral infection subjects affected / exposed occurrences (all)	5 / 107 (4.67%) 5	6 / 109 (5.50%) 6	4 / 111 (3.60%) 4

Gastroenteritis subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	3 / 109 (2.75%) 3	7 / 111 (6.31%) 7
Herpes zoster subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	5 / 109 (4.59%) 5	2 / 111 (1.80%) 2
Metabolism and nutrition disorders			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4	5 / 109 (4.59%) 5	3 / 111 (2.70%) 3
Hyperlipidaemia subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	7 / 109 (6.42%) 7	4 / 111 (3.60%) 4
Diabetes mellitus subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3	6 / 109 (5.50%) 6	3 / 111 (2.70%) 3

<b>Non-serious adverse events</b>	Sprifermin (AS902330) 100 mcg/Placebo (2 cycles)	Sprifermin (AS902330) 100 mcg- 4 Cycles	
Total subjects affected by non-serious adverse events subjects affected / exposed	106 / 111 (95.50%)	107 / 109 (98.17%)	
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	20 / 111 (18.02%) 20	21 / 109 (19.27%) 21	
General disorders and administration site conditions			
Injection site pain subjects affected / exposed occurrences (all)	4 / 111 (3.60%) 4	8 / 109 (7.34%) 8	
Injection site bruising subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2	4 / 109 (3.67%) 4	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	9 / 109 (8.26%) 9	
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2	3 / 109 (2.75%) 3	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	2 / 109 (1.83%) 2	
Investigations C-reactive protein increased subjects affected / exposed occurrences (all)	3 / 111 (2.70%) 3	6 / 109 (5.50%) 6	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	9 / 111 (8.11%) 9	7 / 109 (6.42%) 7	
Contusion subjects affected / exposed occurrences (all)	4 / 111 (3.60%) 4	9 / 109 (8.26%) 9	
Ligament sprain subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2	8 / 109 (7.34%) 8	
Skin abrasion subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	7 / 109 (6.42%) 7	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	13 / 111 (11.71%) 13	18 / 109 (16.51%) 18	
Sciatica subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 7	7 / 109 (6.42%) 7	
Dizziness subjects affected / exposed occurrences (all)	5 / 111 (4.50%) 5	10 / 109 (9.17%) 10	
Hypoaesthesia subjects affected / exposed occurrences (all)	3 / 111 (2.70%) 3	3 / 109 (2.75%) 3	

Memory impairment subjects affected / exposed occurrences (all)	0 / 111 (0.00%) 0	2 / 109 (1.83%) 2	
Eye disorders Cataract subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	4 / 109 (3.67%) 4	
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	6 / 109 (5.50%) 6	
Diarrhoea subjects affected / exposed occurrences (all)	8 / 111 (7.21%) 8	5 / 109 (4.59%) 5	
Gastritis subjects affected / exposed occurrences (all)	4 / 111 (3.60%) 4	6 / 109 (5.50%) 6	
Toothache subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 7	3 / 109 (2.75%) 3	
Dyspepsia subjects affected / exposed occurrences (all)	1 / 111 (0.90%) 1	3 / 109 (2.75%) 3	
Abdominal pain subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	2 / 109 (1.83%) 2	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	2 / 109 (1.83%) 2	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	55 / 111 (49.55%) 55	54 / 109 (49.54%) 54	
Back pain			

subjects affected / exposed	33 / 111 (29.73%)	27 / 109 (24.77%)
occurrences (all)	33	27
Osteoarthritis		
subjects affected / exposed	17 / 111 (15.32%)	17 / 109 (15.60%)
occurrences (all)	17	17
Musculoskeletal pain		
subjects affected / exposed	21 / 111 (18.92%)	21 / 109 (19.27%)
occurrences (all)	21	21
Pain in extremity		
subjects affected / exposed	18 / 111 (16.22%)	20 / 109 (18.35%)
occurrences (all)	18	20
Joint swelling		
subjects affected / exposed	12 / 111 (10.81%)	14 / 109 (12.84%)
occurrences (all)	12	14
Neck pain		
subjects affected / exposed	9 / 111 (8.11%)	7 / 109 (6.42%)
occurrences (all)	9	7
Spinal pain		
subjects affected / exposed	6 / 111 (5.41%)	10 / 109 (9.17%)
occurrences (all)	6	10
Muscle spasms		
subjects affected / exposed	1 / 111 (0.90%)	10 / 109 (9.17%)
occurrences (all)	1	10
Myalgia		
subjects affected / exposed	3 / 111 (2.70%)	6 / 109 (5.50%)
occurrences (all)	3	6
Periarthritis		
subjects affected / exposed	5 / 111 (4.50%)	4 / 109 (3.67%)
occurrences (all)	5	4
Plantar fasciitis		
subjects affected / exposed	4 / 111 (3.60%)	4 / 109 (3.67%)
occurrences (all)	4	4
Tendonitis		
subjects affected / exposed	4 / 111 (3.60%)	4 / 109 (3.67%)
occurrences (all)	4	4
Arthritis		

subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	3 / 109 (2.75%) 3	
<b>Infections and infestations</b>			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	28 / 111 (25.23%) 28	30 / 109 (27.52%) 30	
Nasopharyngitis subjects affected / exposed occurrences (all)	19 / 111 (17.12%) 19	22 / 109 (20.18%) 22	
Urinary tract infection subjects affected / exposed occurrences (all)	13 / 111 (11.71%) 13	17 / 109 (15.60%) 17	
Influenza subjects affected / exposed occurrences (all)	12 / 111 (10.81%) 12	12 / 109 (11.01%) 12	
Cystitis subjects affected / exposed occurrences (all)	9 / 111 (8.11%) 9	10 / 109 (9.17%) 10	
Bronchitis subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	9 / 109 (8.26%) 9	
Pneumonia subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	3 / 109 (2.75%) 3	
Viral infection subjects affected / exposed occurrences (all)	4 / 111 (3.60%) 4	4 / 109 (3.67%) 4	
Gastroenteritis subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 7	2 / 109 (1.83%) 2	
Herpes zoster subjects affected / exposed occurrences (all)	3 / 111 (2.70%) 3	6 / 109 (5.50%) 6	
<b>Metabolism and nutrition disorders</b>			
Hypercholesterolaemia			

subjects affected / exposed	10 / 111 (9.01%)	7 / 109 (6.42%)	
occurrences (all)	10	7	
Hyperlipidaemia			
subjects affected / exposed	6 / 111 (5.41%)	2 / 109 (1.83%)	
occurrences (all)	6	2	
Diabetes mellitus			
subjects affected / exposed	6 / 111 (5.41%)	3 / 109 (2.75%)	
occurrences (all)	6	3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2013	<ul style="list-style-type: none"><li>- Inclusion criterion for joint space width (JSW) of &gt; 3.0 mm was changed to JSW &gt; 2.5 mm based on data from recently published clinical trials</li><li>- Clarified that according to the criteria of the American College of Rheumatology (ACR), subjects should report a history of pain on most days, i.e. more than half of the days of the previous month</li><li>- Modified the drug washout requirement for subjects who are using analgesic/anti-inflammatory drugs to manage OA pain</li><li>- Restriction on the concomitant use of short-term corticosteroids for a condition other than OA was changed to allow for low-dose or short term use of corticosteroids for concomitant medical conditions (e.g., allergic or respiratory conditions)</li><li>- The number of study sites was reduced based on the decision to use a network of sites with extensive experience in conducting these types of OA trials with a well-built history of subject recruitment.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported