Clinical trial results:
A phase II randomized, double-blind, placebo-controlled trial of radium-223 dichloride versus placebo when administered to metastatic HER2 negative hormone receptor positive breast cancer subjects with bone metastases treated with hormonal treatment background therapy.

Summary

EudraCT number	2014-002113-39
Trial protocol	GB ES AT NO CZ DK NL SE PL FI IE FR DE
Global end of trial date	13 August 2019

Results information

Result version number	v1 (current)
This version publication date	03 July 2020
First version publication date	03 July 2020

Trial information

Trial identification

Sponsor protocol code	BAY88-8223/16298

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02258464
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	13 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of radium-223 dichloride in subjects with HER2 negative, hormone receptor positive breast cancer with bone metastases treated with hormonal treatment background therapy.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Taiwan: 2

Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	99
EEA total number of subjects	47

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)	68
From 65 to 84 years	30
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

151 subjects were screened at 69 active centers in 20 countries, the first subject first visit was on 02 Mar 2015 and last subject last visit was on 13 Aug 2019

Pre-assignment

Screening details:

Of the 151 screened subjects, 99 subjects (65.6%) completed screening and were assigned to treatment: 49 in the radium 223 dichloride and 50 in the placebo arm

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Radium 223 dichloride

Arm description:

Subjects treated with a single hormonal agent as background therapy received 50 kBq/kg body weight (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) of Radium 223 dichloride for a maximum of 6 cycles at intervals of 4 weeks

Arm type	Experimental
Investigational medicinal product name	Radium-223 dichloride
Investigational medicinal product code	BAY88-8223
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

50 kBq/kg (55 kBq/kg after implementation of NIST update) body weight every 4 weeks for 6 cycles, injected intravenously as a slow bolus

Arm title	Placebo

Arm description:

Subjects treated with a single hormonal agent as background therapy received isotonic saline (0.9% sodium chloride solution for injection) intravenously for a maximum of 6 cycles at intervals of 4 weeks

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

Dosage and administration details:

Matching placebo (isotonic saline), injected intravenously as a slow bolus

Number of subjects in period 1	Radium 223 dichloride	Placebo
Started	49	50
Completed	32	25
Not completed	17	25
Consent withdrawn by subject	5	4
Study drug never administered	1	1
AE related to clinical disease progression	1	-
AE not related to clinical disease progression	1	3
Progressive disease	9	17

Baseline characteristics

Reporting groups	
Reporting group title	Radium 223 dichloride
Reporting group description:	
Subjects treated with a single hormonal agent as background therapy received 50 kBq/kg body weight (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) of Radium 223 dichloride for a maximum of 6 cycles at intervals of 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects treated with a single hormonal agent as background therapy received isotonic saline (0.9% sodium chloride solution for injection) intravenously for a maximum of 6 cycles at intervals of 4 weeks	

Reporting group values	Radium 223 dichloride	Placebo	Total
Number of subjects	49	50	99
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.08	58.74	
standard deviation	± 11.51	± 11.97	-
Gender categorical Units: Subjects			
Female	49	50	99
Race Units: Subjects			
White	35	40	75
Black or African American	1	0	1
Asian	9	9	18
Not reported	4	1	5
Ethnicity Units: Subjects			
Not Hispanic or Latino	47	47	94
Not reported	2	3	5

End points

End points reporting groups

Reporting group title	Radium 223 dichloride
Reporting group description:	
Subjects treated with a single hormonal agent as background therapy received 50 kBq/kg body weight (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) of Radium 223 dichloride for a maximum of 6 cycles at intervals of 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Subjects treated with a single hormonal agent as background therapy received isotonic saline (0.9% sodium chloride solution for injection) intravenously for a maximum of 6 cycles at intervals of 4 weeks	
Subject analysis set title	Intent to treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
all randomized participants, the primary population for all efficacy analyses was the ITT analysis set	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
all randomized subjects who received at least one dose of study medication (radium 223 dichloride or placebo)	

Primary: Symptomatic skeletal event free survival (SSE-FS)

End point title	Symptomatic skeletal event free survival (SSE-FS)
End point description:	
Time from date of randomization to occurrence of one of the following, whichever happened earlier: 1) an on study SSE, which was defined as the use of EBRT to relieve skeletal symptoms, the occurrence of new symptomatic pathological bone fractures (vertebral or nonvertebral), the occurrence of spinal cord compression, a tumor related orthopedic surgical intervention; or 2) death from any cause	
End point type	Primary
End point timeframe:	
Up to 51 months	

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	50		
Units: months				
median (confidence interval 80%)	30.1 (21.8 to 43.0)	18.4 (9.1 to 28.2)		

Statistical analyses

Statistical analysis title	Analysis based on Kaplan-Meier Curves
Statistical analysis description:	
The null hypothesis that both treatment groups have the same SSE-FS distribution will be tested against the alternative hypothesis that the distribution of SSE-FS time in radium-223 dichloride is different from the placebo group	

Comparison groups	Radium 223 dichloride v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3339 [1]
Method	Logrank
Parameter estimate	Hazard Ratio (Radium 223/Placebo)
Point estimate	0.745
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.504
upper limit	1.102

Notes:

[1] - The SSE-FS was compared using a stratified log-rank test with a 2-sided alpha of 0.2

Secondary: Overall survival

End point title	Overall survival

End point description:

Time from randomization to death from any cause

End point type	Secondary

End point timeframe:

Up to 51 months

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[2]	50[3]		
Units: months				
median (confidence interval 80%)	43 (22.9 to 99999)	32.4 (23.7 to 99999)		

Notes:

[2] - 99999: not estimable due to censored data

[3] - 99999: not estimable due to censored data

Statistical analyses

No statistical analyses for this end point

Secondary: Time to opiate use for cancer pain

End point title	Time to opiate use for cancer pain

End point description:

Interval from the date of randomization to the date of opiate use

End point type	Secondary

End point timeframe:

Up to 51 months

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[4]	49[5]		
Units: months				
median (confidence interval 80%)	21.3 (8.3 to 99999)	20.2 (8.8 to 99999)		

Notes:

[4] - 99999: not estimable due to censored data

[5] - 99999: not estimable due to censored data

Statistical analyses

No statistical analyses for this end point

Secondary: Time to cytotoxic chemotherapy

End point title	Time to cytotoxic chemotherapy

End point description:

Time from the date of randomization to the date of the first cytotoxic chemotherapy

End point type	Secondary

End point timeframe:

Up to 51 months

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	50		
Units: months				
median (confidence interval 80%)	16.0 (14.1 to 22.4)	17.3 (10.9 to 27.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiological progression-free survival (rPFS)

End point title	Radiological progression-free survival (rPFS)

End point description:

Time from the date of randomization to the date of first radiological progression or death (if death occurs before progression)

End point type	Secondary

End point timeframe:

Up to 51 months

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	50		
Units: months				
median (confidence interval 80%)	8.1 (5.7 to 10.6)	5.8 (5.1 to 7.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Improvement Rate

End point title	Pain Improvement Rate

End point description:

The percentage of participants (baseline WPS>=2) with confirmed pain improvement at any time point. Confirmed pain improvement is defined as a 2 point decrease in worst pain score (WPS) from baseline over 2 consecutive assessment periods conducted at least 4 weeks apart

End point type	Secondary

End point timeframe:

Up to 51 months

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	35		
Units: percent				
number (confidence interval 80%)				
Overall (confirmed)	37.5 (25.9 to 50.4)	25.7 (16.2 to 37.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events

End point title	Number of subjects with treatment-emergent adverse events

End point description:

End point type	Secondary

End point timeframe:

From the start of study drug administration until 30 days after the last study medication intake,

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: subjects				
Any TEAE	46	46		
Radium 223/Placebo related TEAEs	21	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with post-treatment adverse events including additional malignancies and chemotherapy related adverse events

End point title	Number of subjects with post-treatment adverse events including additional malignancies and chemotherapy related adverse events

End point description:

End point type	Secondary

End point timeframe:

From 30 days after the last dose of study treatment until the end of study, assessed up to 44 months

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: subjects				
Anaemia	1	0		
Febrile neutropenia	1	0		
Chest pain	1	0		
Fibula fracture	1	0		
Rib fracture	1	0		
Tibia fracture	1	0		
Traumatic fracture	1	0		
Weight decreased	0	1		
Arthralgia	1	0		
Back pain	4	0		
Bone pain	2	3		
Muscle spasms	1	0		
Musculoskeletal chest pain	1	0		
Osteonecrosis of jaw	1	0		
Pain in extremity	1	1		

Pathological fracture	5	4		
Spinal pain	0	3		
Cauda equina syndrome	0	1		
Paraesthesia	0	1		
Spinal cord compression	1	1		
Acute kidney injury	0	1		
Any post-treatment AE	15	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to pain progression

End point title	Time to pain progression

End point description:

Time from randomization to the first date a subject (only in subjects with baseline WPS ≤8) experiences pain progression based on worst pain score (WPS) and analgesic use. Pain progression is defined as an increase of 2 or more points in the "Worst pain in 24 hours" score from baseline observed at 2 consecutive evaluations ≥4 weeks apart or an increase in pain management (IPM) with respect to baseline, whichever occurs first

End point type	Secondary

End point timeframe:

Up to 51 months

End point values	Radium 223 dichloride	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: months				
median (confidence interval 80%)	14.8 (5.9 to 21.3)	8.8 (3.7 to 14.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study drug administration until 30 days after the last study medication intake, assessed up to approximately 7 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Radium 223 dichloride

Reporting group description:

Subjects treated with a single hormonal agent as background therapy received 50 kBq/kg body weight (55 kBq/kg after implementation of National Institute of Standards and Technology [NIST] update) of Radium 223 dichloride for a maximum of 6 cycles at intervals of 4 weeks

Reporting group title	Placebo

Reporting group description:

Subjects treated with a single hormonal agent as background therapy received isotonic saline (0.9% sodium chloride solution for injection) intravenously for a maximum of 6 cycles at intervals of 4 weeks

Serious adverse events	Radium 223 dichloride	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 48 (8.33%)	14 / 49 (28.57%)	
number of deaths (all causes)	18	18	
number of deaths resulting from adverse events	0	1	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fibula fracture			

subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nerve compression			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 48 (2.08%)	3 / 49 (6.12%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			

subjects affected / exposed	1 / 48 (2.08%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Radium 223 dichloride	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 48 (89.58%)	42 / 49 (85.71%)	
Investigations			
Weight decreased			
subjects affected / exposed	3 / 48 (6.25%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 48 (6.25%)	3 / 49 (6.12%)	
occurrences (all)	5	5	
Hot flush			

subjects affected / exposed	0 / 48 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 48 (4.17%)	3 / 49 (6.12%)	
occurrences (all)	3	3	
Headache			
subjects affected / exposed	13 / 48 (27.08%)	4 / 49 (8.16%)	
occurrences (all)	19	4	
Paraesthesia			
subjects affected / exposed	1 / 48 (2.08%)	4 / 49 (8.16%)	
occurrences (all)	1	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 48 (4.17%)	3 / 49 (6.12%)	
occurrences (all)	4	7	
Leukopenia			
subjects affected / exposed	3 / 48 (6.25%)	0 / 49 (0.00%)	
occurrences (all)	6	0	
Neutropenia			
subjects affected / exposed	5 / 48 (10.42%)	0 / 49 (0.00%)	
occurrences (all)	12	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 48 (25.00%)	9 / 49 (18.37%)	
occurrences (all)	15	10	
Influenza like illness			
subjects affected / exposed	3 / 48 (6.25%)	1 / 49 (2.04%)	
occurrences (all)	4	1	
Oedema peripheral			
subjects affected / exposed	3 / 48 (6.25%)	1 / 49 (2.04%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	0 / 48 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	5 / 48 (10.42%)	2 / 49 (4.08%)	
occurrences (all)	6	3	
Diarrhoea			
subjects affected / exposed	10 / 48 (20.83%)	7 / 49 (14.29%)	
occurrences (all)	15	10	
Constipation			
subjects affected / exposed	4 / 48 (8.33%)	4 / 49 (8.16%)	
occurrences (all)	5	4	
Nausea			
subjects affected / exposed	12 / 48 (25.00%)	9 / 49 (18.37%)	
occurrences (all)	18	13	
Vomiting			
subjects affected / exposed	7 / 48 (14.58%)	7 / 49 (14.29%)	
occurrences (all)	7	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 48 (2.08%)	4 / 49 (8.16%)	
occurrences (all)	1	4	
Dyspnoea			
subjects affected / exposed	3 / 48 (6.25%)	0 / 49 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 48 (20.83%)	11 / 49 (22.45%)	
occurrences (all)	13	17	
Back pain			
subjects affected / exposed	10 / 48 (20.83%)	7 / 49 (14.29%)	
occurrences (all)	14	10	
Bone pain			
subjects affected / exposed	10 / 48 (20.83%)	7 / 49 (14.29%)	
occurrences (all)	10	13	
Musculoskeletal pain			
subjects affected / exposed	6 / 48 (12.50%)	4 / 49 (8.16%)	
occurrences (all)	10	4	
Myalgia			

subjects affected / exposed	4 / 48 (8.33%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Neck pain			
subjects affected / exposed	4 / 48 (8.33%)	1 / 49 (2.04%)	
occurrences (all)	5	1	
Pain in extremity			
subjects affected / exposed	5 / 48 (10.42%)	6 / 49 (12.24%)	
occurrences (all)	7	8	
Pathological fracture			
subjects affected / exposed	3 / 48 (6.25%)	3 / 49 (6.12%)	
occurrences (all)	3	3	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 48 (8.33%)	2 / 49 (4.08%)	
occurrences (all)	4	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 48 (6.25%)	3 / 49 (6.12%)	
occurrences (all)	3	3	
Urinary tract infection			
subjects affected / exposed	2 / 48 (4.17%)	4 / 49 (8.16%)	
occurrences (all)	2	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 48 (6.25%)	5 / 49 (10.20%)	
occurrences (all)	3	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2014	Amendment 1 (global amendment) forming integrated protocol Version 2.0
29 April 2015	Amendment 2 (global amendment) forming integrated protocol Version 3.0
29 July 2015	Amendment 4 (global amendment) forming integrated protocol Version 4.0
11 March 2016	Amendment 5 (global amendment) forming integrated protocol Version 5.0
11 July 2016	Amendment 6 (global amendment) forming integrated protocol Version 6.0
23 May 2017	Amendment 7 (global amendment) forming integrated protocol Version 7.0
03 April 2018	Amendment 8 (global amendment) forming current integrated protocol Version 8.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to the premature enrollment discontinuation, reduced sample size, and potentially curtailed active follow up, the planned number of SSE FS events was not achieved, limiting the assessment of the primary efficacy endpoint.

Notes: