



Clinical trial results:

A randomized, double-blind, placebo-controlled, multicenter Phase II trial investigating two doses of EMD 525797 in subjects with asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (mCRPC)

Summary

EudraCT number	2010-021529-11
Trial protocol	BE DE NL ES SK
Global end of trial date	08 July 2014

Results information

Result version number	v1
This version publication date	13 June 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	EMR 62242-006
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01360840
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Str. 250, Darmstadt, Germany, 64293
Public contact	Communication Centre merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre merck KGaA, Merck KGaA, +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	Interim
Date of interim/final analysis	30 April 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2013
Global end of trial reached?	Yes
Global end of trial date	08 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate the clinical anti-tumor activity of EMD 525797 administered as 1-hour intravenous infusion every 3 weeks in terms of progression free survival (PFS) time in subjects with asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (mCRPC).

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	01 April 2011
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	Australia: 11
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Russian Federation: 42
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	180
EEA total number of subjects	89

Notes:

Subjects enrolled per age group

In utero	0
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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)	49
From 65 to 84 years	125
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

First/Last subject (informed consent): April 2011/December 2012. Study completion date: July 2014. Clinical data cut-off: 30 April 2013. Subjects were recruited in 11 countries (Australia, Belgium, Canada, France, Germany, Netherlands, Poland, Russia, South Africa, Spain, and USA) across the globe in 65 centers.

Pre-assignment

Screening details:

Enrolled: 283 screened for eligibility; 103 were excluded (mainly non-fulfillment of inclusion or exclusion criteria). 180 subjects were assigned to the treatment groups., However out of these 180 subject, two subjects did not receive study drug administration.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + SoC

Arm description:

Subjects were administered with placebo 0.9% sodium chloride as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

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

Dosage and administration details:

Subjects were administered with placebo 0.9% sodium chloride as a 1-hour intravenous infusion every 3 Weeks. Subjects also received SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists).

Arm title	EMD 525797 750 mg + SoC
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Arm description:

Subjects were administered with EMD 525797 at a dose of 750 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

Arm type	Experimental
Investigational medicinal product name	EMD 525797
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with EMD 525797 at a dose of 750 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks.

Arm title	EMD 525797 1500 mg + SoC
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Arm description:

Subjects were administered with EMD 525797 at a dose of 1500 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

Arm type	Experimental
Investigational medicinal product name	EMD 525797
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with EMD 525797 at a dose of 1500 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks.

Number of subjects in period 1	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC
Started	60	60	60
Completed	50	50	51
Not completed	10	10	9
Ongoing at data cut-off	10	10	9

Baseline characteristics

Reporting groups

Reporting group title	Placebo + SoC
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Reporting group description:

Subjects were administered with placebo 0.9% sodium chloride as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

Reporting group title	EMD 525797 750 mg + SoC
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Reporting group description:

Subjects were administered with EMD 525797 at a dose of 750 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

Reporting group title	EMD 525797 1500 mg + SoC
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Reporting group description:

Subjects were administered with EMD 525797 at a dose of 1500 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

Reporting group values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC
Number of subjects	60	60	60
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	69.9 ± 8.43	69 ± 7.31	70 ± 8.88
Gender, Male/Female Units: Subjects			
Female	0	0	0
Male	60	60	60

Reporting group values	Total		
Number of subjects	180		
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	-		
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Gender, Male/Female			
Units: Subjects			
Female	0		
Male	180		

End points

End points reporting groups

Reporting group title	Placebo + SoC
Reporting group description: Subjects were administered with placebo 0.9% sodium chloride as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.	
Reporting group title	EMD 525797 750 mg + SoC
Reporting group description: Subjects were administered with EMD 525797 at a dose of 750 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.	
Reporting group title	EMD 525797 1500 mg + SoC
Reporting group description: Subjects were administered with EMD 525797 at a dose of 1500 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.	

Primary: Progression free survival (PFS) time

End point title	Progression free survival (PFS) time
End point description: PFS was defined as time from randomization until the first documented sign of objective radiographic disease progression (ORDP) or death from any cause. Death was considered as an event only if it was reported within 12 weeks after last tumor assessment without progression. ORDP was defined as: Bone lesion progression (2 or more new bone lesions compared to baseline) assessed with bone scintigraphy. Assessment was based on Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v1.0) modified as per Prostate Cancer Working Group 2 (PCWG-2); Soft-tissue lesion progression assessed with CT scans according to RECIST v1.0 modified as per PCWG-2; Presence of skeletal events defined as cord compression/fracture documented via a scheduled or unscheduled radiographic assessment triggered by increased pain or other signs and/or symptoms, based on the investigator's discretion; Non-radiological events, including emergency bone irradiation and surgery, were not investigated.	
End point type	Primary
End point timeframe: Up to data cut-off date (30 April 2013)	

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	60	60	
Units: months				
median (confidence interval 95%)	3.3 (2.8 to 4.8)	3.4 (2.8 to 5.6)	4.3 (2.8 to 6.6)	

Statistical analyses

Statistical analysis title	Placebo + SoC versus EMD 525797 750 mg + SoC
Comparison groups	Placebo + SoC v EMD 525797 750 mg + SoC
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.39

Statistical analysis title	Placebo + SoC versus EMD 525797 1500 mg + SoC
Comparison groups	Placebo + SoC v EMD 525797 1500 mg + SoC
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.26

Secondary: Overall survival

End point title	Overall survival
End point description:	
Overall Survival was defined as the time from the date of randomization to the date of death from any cause. Here, the value "99999.9" indicates that the endpoint was not evaluable.	
End point type	Secondary
End point timeframe:	
Up to data cut-off date (30 April 2013)	

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	60	60	
Units: months				
median (confidence interval 95%)	99999.9 (14.8 to 99999.9)	99999.9 (12.4 to 99999.9)	99999.9 (14.4 to 99999.9)	

Statistical analyses

Statistical analysis title	Placebo + SoC versus EMD 525797 750 mg + SoC
Comparison groups	Placebo + SoC v EMD 525797 750 mg + SoC
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	2.31

Statistical analysis title	Placebo + SoC versus EMD 525797 1500 mg + SoC
Comparison groups	Placebo + SoC v EMD 525797 1500 mg + SoC
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	2.15

Secondary: Time to tumor progression

End point title	Time to tumor progression
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End point description:

Time to tumor progression was defined as the time from the date of randomization to the date of ORDP. ORDP was defined as: Bone lesion progression (2 or more new bone lesions compared to baseline) assessed with bone scintigraphy, which had to be confirmed by bone scintigraphy 6 weeks later if subjects remained asymptomatic or mildly symptomatic. Assessments were to be based on RECIST v1.0 modified according to PCWG-2; Soft-tissue lesion progression assessed with CT scans according to RECIST v1.0 modified as per PCWG-2; Presence of skeletal events defined as cord compression or fracture documented via a scheduled or unscheduled radiographic assessment triggered by increased

pain or other signs and/or symptoms, based on the investigator's discretion; Non-radiological events, including emergency bone irradiation and surgery, were not investigated.

End point type	Secondary
End point timeframe:	
Up to data cut-off date (30 April 2013)	

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	60	60	
Units: months				
median (confidence interval 95%)	3.3 (2.8 to 5.4)	3.4 (2.8 to 5.6)	4.6 (2.8 to 6.9)	

Statistical analyses

Statistical analysis title	Placebo + SoC versus EMD 525797 750 mg + SoC
Comparison groups	Placebo + SoC v EMD 525797 750 mg + SoC
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.44

Statistical analysis title	Placebo + SoC versus EMD 525797 1500 mg + SoC
Comparison groups	Placebo + SoC v EMD 525797 1500 mg + SoC
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.27

Secondary: Number of subjects with presence of tumor response and disease control (DC) in soft tissue lesions

End point title	Number of subjects with presence of tumor response and disease control (DC) in soft tissue lesions
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End point description:

Presence of tumor response in soft tissue lesions was defined as the presence of at least 1 confirmed complete response (CR) or confirmed partial response (PR) in soft tissue lesions, documented by computed tomography (CT) scans. Presence of DC in soft tissue lesions was defined as the presence of at least 1 confirmed CR or confirmed PR or stable disease (SD) lasting at least 12 weeks after randomization. Tumor response assessments were based on RECIST v1.0 modified according to the PCWG-2. The response was evaluated for subjects with measurable disease at baseline. According to RECIST v1.0, CR=disappearance of all target and non-target lesions; PR=at least 30% decrease in the sum of the longest diameter of target lesions and non-complete response/non-progressive disease in non-target lesions. This endpoint was assessed in ITT analysis set subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Up to data cut-off date (30 April 2013)

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	22	24	
Units: Subjects				
Tumor response	1	0	1	
Disease control	2	3	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with new bone lesions compared to baseline

End point title	Number of subjects with new bone lesions compared to baseline
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End point description:

New bone lesions were evaluated by bone scintigraphy for subjects with bone lesions at baseline. This endpoint was assessed in ITT analysis set subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Up to data cut-off date (30 April 2013)

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	57	57	
Units: Subjects	40	34	34	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Presence of DC in bone lesions

End point title	Number of subjects with Presence of DC in bone lesions
End point description: Presence of DC in bone lesions was defined as the appearance of less than 2 new bone lesions, documented by bone scintigraphy. This endpoint was assessed in ITT analysis set.	
End point type	Secondary
End point timeframe: At Weeks 13, 19 and 25	

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	60	60	
Units: Subjects				
Week 13	4	7	7	
Week 19	2	7	6	
Week 25	2	4	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Bone and soft tissue lesions Composite Tumor Response

End point title	Bone and soft tissue lesions Composite Tumor Response
End point description: Bone and soft tissue lesions composite tumor response was defined as the presence of both a confirmed CR or PR, documented by CT scans, and a DC in bone lesions, documented by bone scintigraphy. CR was defined as disappearance of all target and non-target lesions and PR was defined as at least 30% decrease in the sum of the longest diameter of target lesions and non-complete response/non-progressive disease in non-target lesions. Presence of DC in bone lesions was defined as the appearance of less than 2 new bone lesions.	
End point type	Secondary
End point timeframe: Up to data cut-off date (30 April 2013)	

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	60	60	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with presence of skeletal related events

End point title	Number of subjects with presence of skeletal related events
End point description:	
Presence of skeletal related events was defined as cord compression or fracture documented via a scheduled or unscheduled radiographic assessment triggered by increased pain or other signs and/or symptoms at the investigator discretion. Non-radiological events, including emergency bone irradiation and surgery, were not investigated. This endpoint was assessed in ITT analysis set.	
End point type	Secondary
End point timeframe:	
Up to data cut-off date (30 April 2013)	

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	60	60	
Units: Subjects				
number (not applicable)	2	8	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Presence of prostate specific antigen (PSA) response

End point title	Number of subjects with Presence of prostate specific antigen (PSA) response
End point description:	
PSA response was defined as a decrease greater than 50 percent (%) in PSA value from baseline for 2 consecutive evaluations greater than or equal to ($\geq$) 3 Weeks apart. This endpoint was assessed in ITT analysis set subjects who were evaluable for this outcome measure.	
End point type	Secondary

End point timeframe:
Up to data cut-off date (30 April 2013)

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	58	60	
Units: Subjects	3	6	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Percentage change from baseline in PSA serum concentration

End point title	Minimum Percentage change from baseline in PSA serum concentration
End point description: This endpoint was assessed in ITT analysis set subjects who were evaluable for this outcome measure.	
End point type	Secondary
End point timeframe: Up to data cut-off date (30 April 2013)	

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	60	
Units: Percent change				
arithmetic mean (standard deviation)	24 ($\pm$ 86.156)	35.65 ($\pm$ 127.677)	14.7 ($\pm$ 50.841)	

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Percentage change from baseline in the number of circulating tumor cells (CTCs)

End point title	Minimum Percentage change from baseline in the number of circulating tumor cells (CTCs)
End point description: This endpoint was assessed in ITT analysis set subjects who were evaluable for this outcome measure.	
End point type	Secondary

End point timeframe:

Up to data cut-off date (30 April 2013)

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	27	22	
Units: Percent change				
arithmetic mean (standard deviation)	49.02 (± 127.643)	354.74 (± 1038.195)	280.58 (± 482.653)	

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Percentage change from previous time point in CTC

End point title	Minimum Percentage change from previous time point in CTC
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End point description:

This endpoint was assessed in ITT analysis set subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Up to data cut-off date (30 April 2013)

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	34	30	
Units: Percent change				
arithmetic mean (standard deviation)	9.54 (± 103.225)	223.97 (± 868.941)	179.11 (± 446.428)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Any treatment emergent adverse events (TEAEs), Serious TEAEs, TEAEs Leading to Death, and TEAEs Leading to Discontinuation

End point title	Number of Subjects With Any treatment emergent adverse events (TEAEs), Serious TEAEs, TEAEs Leading to Death, and TEAEs Leading to Discontinuation
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End point description:

An AE was defined as any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. A SAE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect. TEAEs were defined as those AEs that started between first dose of study drug and up to 50 days after last dose. This endpoint was assessed in the safety analysis set which included all the randomized subjects who received at least 1 dose of planned trial treatment and had at least one safety assessment following the trial treatment.

End point type	Secondary
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End point timeframe:

Up to data cut-off date (30 April 2013)

End point values	Placebo + SoC	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	58	60	
Units: Subjects				
TEAEs	55	49	53	
Serious TEAEs	16	13	14	
TEAEs leading to death	2	2	3	
TEAEs Leading to Permanent Discontinuation	5	11	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: Clearance of intravenously administered EMD 525797 after first dose (CL) and clearance in steady state of EMD52597 after fifth dose (CLss)

End point title	Pharmacokinetic Parameter: Clearance of intravenously administered EMD 525797 after first dose (CL) and clearance in steady state of EMD52597 after fifth dose (CLss) ^[1]
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End point description:

The apparent total body clearance of drug following intravenous administration (CL); The apparent total body clearance of drug at steady state following intravenous administration (CLss). This endpoint was assessed in pharmacokinetic analysis set (PKA) which included all the randomized subjects who received at least the first dose of the trial drug and provided sufficient data for a concentration time profile for EMD 525797. "n" signifies the number of subjects evaluable for each category in the evaluated group, respectively.

End point type	Secondary
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End point timeframe:

Week1 until pre-dose of Week 4: First dose; Week 13 until pre-dose Week 16: Fifth dose

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is reported in only EMD 52597 750 mg+SoC and EMD 52597 1500 mg+SoC as per planned analysis.

End point values	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6		
Units: Liter per hour				
arithmetic mean (standard deviation)				
First dose: CL (n=4, 6)	0.017 (± 0.007)	0.013 (± 0.003)		
Fifth dose: CLss (n=2, 4)	0.017 (± 0.002)	0.01 (± 0.001)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter: Volume of distribution of EMD 525797 after the first dose (V) and in steady state after the fifth dose (Vss) of intravenous infusion

End point title	Pharmacokinetic Parameter: Volume of distribution of EMD 525797 after the first dose (V) and in steady state after the fifth dose (Vss) of intravenous infusion ^[2]
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End point description:

The apparent volume of distribution during the terminal phase following intravenous administration (V). The estimate of the apparent volume of distribution at steady state following intravenous administration (Vss). This endpoint was assessed in PKA. "n" signifies the number of subjects evaluable for each category in the evaluated group, respectively. The value "99999.9" here indicates the standard deviation for this parameter which was not evaluable.

End point type	Secondary
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End point timeframe:

Week1 until pre-dose of Week 4: First dose; Week 13 until pre-dose Week 16: Fifth dose

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is reported in only EMD 52597 750 mg+SoC and EMD 52597 1500 mg+SoC as per planned analysis.

End point values	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6		
Units: liter				
arithmetic mean (standard deviation)				
First dose (n=4, 6)	4.55 (± 1.02)	4.6 (± 0.74)		
Fifth dose (n=2, 4)	4.81 (± 99999.9)	5.18 (± 0.56)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: To explore the relationship between number and/or changes of numbers of biomarker and the clinical outcome

End point title	To explore the relationship between number and/or changes of numbers of biomarker and the clinical outcome ^[3]
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End point description:

End point type	Other pre-specified
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End point timeframe:

Up to data cut-off date (30 April 2013)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is reported in only EMD 52597 750 mg+SoC and EMD 52597 1500 mg+SoC as per planned analysis.

End point values	EMD 525797 750 mg + SoC	EMD 525797 1500 mg + SoC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: Number of biomarkers				

Notes:

[4] - Data for this outcome measure was presented graphically as per planned analysis.

[5] - Data for this outcome measure was presented graphically as per planned analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the initiation of the trial treatment until 30 days after last administration of trial treatment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Placebo + SoC
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Reporting group description:

Subjects were administered with placebo 0.9% sodium chloride as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

Reporting group title	EMD 525797 1500 mg + SoC
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Reporting group description:

Subjects were administered with EMD 525797 at a dose of 1500 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

Reporting group title	EMD 525797 750 mg + SoC
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Reporting group description:

Subjects were administered with EMD 525797 at a dose of 750 mg (diluted with 0.9% sodium chloride) as a 1-hour intravenous infusion every 3 Weeks until disease progression or unacceptable toxicity, whichever comes first, unless the subject stopped the trial treatment for other reasons. All the subjects followed the SoC consisting of the continued treatment with luteinizing-hormone releasing hormone agonists (or antagonists). In order to avoid any confounding effects, bisphosphonate treatment was initiated 2 days before start of treatment with EMD 525797.

Serious adverse events	Placebo + SoC	EMD 525797 1500 mg + SoC	EMD 525797 750 mg + SoC
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 60 (26.67%)	14 / 60 (23.33%)	13 / 58 (22.41%)
number of deaths (all causes)	2	2	2
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Fatigue			
subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	0 / 58 (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
Disease progression			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Gait disturbance			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Infusion site extravasation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Femur fracture			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Spinal compression fracture			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Arrhythmia			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Balance disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Headache			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	0 / 58 (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
Dysaesthesia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiduritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Ischaemic stroke			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 60 (1.67%)	3 / 60 (5.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (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
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rectal haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Periodontitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (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
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pemphigoid			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (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
Haematuria			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (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
Renal failure			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Urinary retention			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Muscular weakness			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	0 / 58 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (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 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis orbital			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (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
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Pyelonephritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (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
Toxic shock syndrome			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolism and nutrition disorders			

Hyperkalaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo + SoC	EMD 525797 1500 mg + SoC	EMD 525797 750 mg + SoC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 60 (88.33%)	53 / 60 (88.33%)	47 / 58 (81.03%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone neoplasm malignant			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Skin papilloma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Squamous cell carcinoma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Tumour pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Tumour invasion			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hot flush			
subjects affected / exposed	3 / 60 (5.00%)	2 / 60 (3.33%)	2 / 58 (3.45%)
occurrences (all)	3	2	2
Hypertension			

subjects affected / exposed	3 / 60 (5.00%)	2 / 60 (3.33%)	1 / 58 (1.72%)
occurrences (all)	4	2	3
Hypotension			
subjects affected / exposed	2 / 60 (3.33%)	1 / 60 (1.67%)	2 / 58 (3.45%)
occurrences (all)	2	1	2
Orthostatic hypertension			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Orthostatic hypotension			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Peripheral coldness			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	9 / 60 (15.00%)	6 / 60 (10.00%)	3 / 58 (5.17%)
occurrences (all)	15	11	3
Chest pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	2 / 58 (3.45%)
occurrences (all)	0	1	2
Crying			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	12 / 60 (20.00%)	9 / 60 (15.00%)	10 / 58 (17.24%)
occurrences (all)	14	9	18
Feeling hot			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	2
Gait disturbance			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Hypothermia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	4 / 60 (6.67%)	3 / 60 (5.00%)	8 / 58 (13.79%)
occurrences (all)	6	5	8
Malaise			
subjects affected / exposed	3 / 60 (5.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	3	0	1
Oedema peripheral			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	7 / 58 (12.07%)
occurrences (all)	1	2	8
Non-Cardiac chest pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	0	1	2
Spinal pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	2 / 58 (3.45%)
occurrences (all)	1	1	2
Pain			
subjects affected / exposed	1 / 60 (1.67%)	3 / 60 (5.00%)	2 / 58 (3.45%)
occurrences (all)	1	3	2
Pyrexia			
subjects affected / exposed	2 / 60 (3.33%)	4 / 60 (6.67%)	4 / 58 (6.90%)
occurrences (all)	2	9	5
Temperature intolerance			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			

Gynaecomastia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Balanitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Pelvic pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Penile pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Testicular pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Perineal pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 60 (1.67%)	5 / 60 (8.33%)	5 / 58 (8.62%)
occurrences (all)	1	5	6
Dysphonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)	3 / 60 (5.00%)	3 / 58 (5.17%)
occurrences (all)	2	3	3
Epistaxis			
subjects affected / exposed	1 / 60 (1.67%)	3 / 60 (5.00%)	1 / 58 (1.72%)
occurrences (all)	1	3	2
Dyspnoea exertional			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	1	1	1
Oropharyngeal pain			

subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	1	1	0
Nasal congestion			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	1	1	1
Haemoptysis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Rhinorrhoea			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Sinus congestion			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	1	1	1
Sputum retention			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Mood altered			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	3 / 60 (5.00%)	3 / 60 (5.00%)	2 / 58 (3.45%)
occurrences (all)	3	3	2
Initial insomnia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0

Depression			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	1	1	1
Stress			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	1	1	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	2 / 58 (3.45%)
occurrences (all)	1	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 60 (5.00%)	4 / 60 (6.67%)	1 / 58 (1.72%)
occurrences (all)	4	5	1
Blood cholesterol increased			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	1	1	0
Blood creatine increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 60 (1.67%)	3 / 60 (5.00%)	2 / 58 (3.45%)
occurrences (all)	1	4	2
Blood potassium increased			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Blood urine present			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	2
Blood urea increased			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
C-Reactive protein increased			
subjects affected / exposed	0 / 60 (0.00%)	3 / 60 (5.00%)	1 / 58 (1.72%)
occurrences (all)	0	3	1
Cardiac murmur			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Calcium ionised decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Gamma-Glutamyltransferase increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	3	0	1
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 60 (0.00%)	3 / 60 (5.00%)	0 / 58 (0.00%)
occurrences (all)	0	3	0
Electrocardiogram st-t segment abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Fibrin d dimer increased			
subjects affected / exposed	4 / 60 (6.67%)	3 / 60 (5.00%)	2 / 58 (3.45%)
occurrences (all)	5	5	3
Lymphocyte count decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Liver function test abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
International normalised ratio decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Haemoglobin decreased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	1	3	0
Weight decreased			
subjects affected / exposed	6 / 60 (10.00%)	5 / 60 (8.33%)	1 / 58 (1.72%)
occurrences (all)	6	5	1
Prostatic specific antigen increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 60 (3.33%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	2	1	1
Excoriation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Hand fracture			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Skin wound			

subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Cardiac disorders			
Angina pectoris subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Bradycardia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Palpitations subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Sinus bradycardia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Nervous system disorders			
Amnesia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Cervical root pain			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Burning sensation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Depressed level of consciousness			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	2 / 60 (3.33%)	3 / 60 (5.00%)	1 / 58 (1.72%)
occurrences (all)	2	3	1
Disturbance in attention			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Epiduritis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	1 / 60 (1.67%)	3 / 60 (5.00%)	1 / 58 (1.72%)
occurrences (all)	1	3	1
Dysaesthesia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Head discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	5 / 60 (8.33%)	2 / 60 (3.33%)	1 / 58 (1.72%)
occurrences (all)	6	2	1
Neuropathy peripheral			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Memory impairment			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			

subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	1 / 58 (1.72%)
occurrences (all)	0	2	1
Paraesthesia			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	0 / 58 (0.00%)
occurrences (all)	0	4	0
Spinal cord compression			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	1 / 60 (1.67%)	2 / 60 (3.33%)	0 / 58 (0.00%)
occurrences (all)	1	2	0
Paresis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Paraplegia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Vascular encephalopathy			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 60 (16.67%)	13 / 60 (21.67%)	6 / 58 (10.34%)
occurrences (all)	16	25	7
Anaemia of chronic disease			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Anaemia macrocytic			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	6	0

Anaemia of malignant disease subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Haemorrhagic anaemia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Leukopenia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	1 / 60 (1.67%) 2	0 / 58 (0.00%) 0
Leukocytosis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Hypochromic anaemia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Lymphopenia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 5
Paratracheal lymphadenopathy subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	3 / 58 (5.17%) 4
Ear and labyrinth disorders			
Hypoacusis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Tinnitus subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Vertigo			

subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	2 / 60 (3.33%) 2	2 / 58 (3.45%) 2
Eye disorders			
Asthenopia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Eye pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Ocular hyperaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Visual acuity reduced			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	1	1	1
Vision blurred			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Scleral haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	2 / 60 (3.33%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	2	1	0
Abdominal pain upper			

subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	1 / 58 (1.72%)
occurrences (all)	0	3	1
Abdominal pain lower			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Aphthous stomatitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Cheilitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	7 / 60 (11.67%)	3 / 60 (5.00%)	6 / 58 (10.34%)
occurrences (all)	9	6	7
Colitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Dental caries			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	3 / 58 (5.17%)
occurrences (all)	2	0	3
Diarrhoea			
subjects affected / exposed	5 / 60 (8.33%)	3 / 60 (5.00%)	9 / 58 (15.52%)
occurrences (all)	5	3	9
Eructation			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Haematochezia			

subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 60 (3.33%)	6 / 60 (10.00%)	6 / 58 (10.34%)
occurrences (all)	3	7	8
Pancreatitis acute			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0
Odynophagia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Periodontitis			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	0 / 58 (0.00%)
occurrences (all)	0	3	0
Paraesthesia oral			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Parotid gland enlargement			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Peptic ulcer			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Retching			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Proctitis			

subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Stomatitis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Proctalgia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	3 / 60 (5.00%) 5	4 / 58 (6.90%) 5
Hepatobiliary disorders Cholecystitis acute subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Cholelithiasis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Hepatomegaly subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Skin and subcutaneous tissue disorders Actinic keratosis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Angioedema subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Dermatitis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Ecchymosis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Dry skin			

subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	1 / 58 (1.72%)
occurrences (all)	0	2	1
Dermatitis bullous			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Eczema asteatotic			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 60 (0.00%)	3 / 60 (5.00%)	1 / 58 (1.72%)
occurrences (all)	0	5	1
Generalised erythema			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	1	0	2
Hypertrichosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Intertrigo			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Lentigo			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Pemphigus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	2
Papule			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Pruritus			

subjects affected / exposed	1 / 60 (1.67%)	6 / 60 (10.00%)	4 / 58 (6.90%)
occurrences (all)	1	6	4
Pruritus generalised			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	2 / 58 (3.45%)
occurrences (all)	0	3	2
Rash			
subjects affected / exposed	1 / 60 (1.67%)	5 / 60 (8.33%)	3 / 58 (5.17%)
occurrences (all)	1	6	3
Rash generalised			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	3 / 58 (5.17%)
occurrences (all)	0	3	5
Skin hyperpigmentation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	1	1	1
Subcutaneous nodule			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	6
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	3	2	0

Calculus urinary			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Dysuria			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 58 (1.72%)
occurrences (all)	1	1	1
Haematuria			
subjects affected / exposed	3 / 60 (5.00%)	3 / 60 (5.00%)	4 / 58 (6.90%)
occurrences (all)	3	4	4
Proteinuria			
subjects affected / exposed	1 / 60 (1.67%)	2 / 60 (3.33%)	1 / 58 (1.72%)
occurrences (all)	1	2	2
Nocturia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Leukocyturia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Hydronephrosis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	2 / 60 (3.33%)	2 / 60 (3.33%)	0 / 58 (0.00%)
occurrences (all)	2	2	0
Renal failure acute			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Renal pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Stress urinary incontinence			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Ureteric obstruction			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0

Urinary incontinence subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Urinary retention subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	2 / 58 (3.45%) 2
Urinary tract obstruction subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 7	7 / 60 (11.67%) 8	7 / 58 (12.07%) 8
Back pain subjects affected / exposed occurrences (all)	10 / 60 (16.67%) 12	6 / 60 (10.00%) 10	9 / 58 (15.52%) 10
Bone pain subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 11	6 / 60 (10.00%) 12	6 / 58 (10.34%) 10
Bone swelling subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Bunion subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Cervical spinal stenosis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Flank pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 2	1 / 60 (1.67%) 3	1 / 58 (1.72%) 1
Groin pain subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Intervertebral disc degeneration			

subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Mobility decreased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	2 / 60 (3.33%)	4 / 60 (6.67%)	1 / 58 (1.72%)
occurrences (all)	2	8	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	3 / 58 (5.17%)
occurrences (all)	1	1	3
Musculoskeletal discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	3 / 60 (5.00%)	3 / 60 (5.00%)	6 / 58 (10.34%)
occurrences (all)	3	3	7
Myalgia			
subjects affected / exposed	4 / 60 (6.67%)	4 / 60 (6.67%)	3 / 58 (5.17%)
occurrences (all)	5	7	6
Neck pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	3 / 58 (5.17%)
occurrences (all)	1	1	3
Osteoarthritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Osteopenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	4 / 60 (6.67%)	3 / 60 (5.00%)	8 / 58 (13.79%)
occurrences (all)	5	4	11
Spinal osteoarthritis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Pain in jaw			

subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Trigger finger subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	1 / 58 (1.72%) 1
Infections and infestations			
Anal fungal infection subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Fungal oesophagitis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Cystitis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	2 / 60 (3.33%) 2	0 / 58 (0.00%) 0
Herpes simplex subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Fungal skin infection subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Influenza subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4	0 / 60 (0.00%) 0	1 / 58 (1.72%) 2
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	2 / 60 (3.33%) 2	5 / 58 (8.62%) 5
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	2 / 60 (3.33%) 2	0 / 58 (0.00%) 0

Oral fungal infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Perineal infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Pyelonephritis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)	2 / 60 (3.33%)	1 / 58 (1.72%)
occurrences (all)	0	2	1
Tooth abscess			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Skin candida			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Wound infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Wound sepsis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0

Urinary tract infection subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	1 / 60 (1.67%) 1	3 / 58 (5.17%) 3
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 5	4 / 60 (6.67%) 4	8 / 58 (13.79%) 10
Dehydration subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	1 / 60 (1.67%) 1	1 / 58 (1.72%) 2
Fluid overload subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Glucose tolerance impaired subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 60 (1.67%) 1	0 / 58 (0.00%) 0
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	3 / 60 (5.00%) 4	2 / 58 (3.45%) 2
Gout subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	1 / 58 (1.72%) 1
Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 3	1 / 60 (1.67%) 1	1 / 58 (1.72%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	2 / 60 (3.33%) 4	0 / 58 (0.00%) 0
Hypermagnesaemia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	0 / 60 (0.00%) 0	0 / 58 (0.00%) 0
Hypoalbuminaemia			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	3 / 60 (5.00%)	7 / 60 (11.67%)	1 / 58 (1.72%)
occurrences (all)	3	8	1
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Vitamin d deficiency			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	3	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2011	The purpose of this protocol amendment was to add safety assessments for increased subject safety and safety data validity, to add PK assessments, and to add immunogenicity assessment.
20 October 2011	The purpose of this protocol amendment was to: Change the statistical method of randomization from Bayesian adaptive randomization to randomization with an allocation ratio of 1:1:1, reduce the number of blood samples taken for biomarker analyses, modify inclusion criteria, and modify ECG recording.
30 August 2012	The purpose of this protocol amendment was to: Decrease the sample size from 216 to 165 randomized subjects and to change the primary analysis cut-off date, and to adapt the wording of the primary objective of the trial.

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.

This trial was prematurely terminated as primary endpoint of the trial i.e. Progression Free Survival, was not met with respect to pre-defined proof of concept criteria. A decision was taken to terminate this trial.

Notes: