

**Clinical trial results:****A Phase 1b/2 Study of Safety and Efficacy of MLN0128 (Dual TORC1/2 Inhibitor) in Combination With Exemestane or Fulvestrant Therapy in Postmenopausal Women With ER+/HER2- Advanced or Metastatic Breast Cancer That Has Progressed on Treatment With Everolimus in Combination With Exemestane or Fulvestrant****Summary**

EudraCT number	2014-001921-34
Trial protocol	BE FR
Global end of trial date	03 July 2018

Results information

Result version number	v2 (current)
This version publication date	08 May 2020
First version publication date	14 July 2019
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	C31001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02049957
WHO universal trial number (UTN)	U1111-1195-3894

Notes:

Sponsors

Sponsor organisation name	Takeda Oncology
Sponsor organisation address	40 Landsdowne Street, Cambridge, United States, 02139
Public contact	Medical Director, Takeda Oncology, +1 8778253327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Takeda Oncology, +1 8778253327, clinicaltrialregistry@tpna.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	03 July 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1b

- To evaluate the safety and tolerability of MLN0128 in combination with either exemestane or fulvestrant.

Phase 2

- To evaluate the antitumor activity by clinical benefit rate (CBR) at 16 weeks (CBR-16 is defined as the proportion of patients who achieve complete response [CR] or partial response of any duration, or have stable disease [SD] at 16 weeks) of treatment with MLN0128 in combination with either exemestane or fulvestrant.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2014
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	United States: 95
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Belgium: 7
Worldwide total number of subjects	118
EEA total number of subjects	23

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)	83
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 40 investigative sites in Belgium, France and the United States from 13 February 2014 to 03 July 2019.

Pre-assignment

Screening details:

Postmenopausal women with estrogen receptor positive/human epidermal growth factor receptor-2 negative advanced/metastatic breast cancer who progressed with everolimus (everolimus sensitive-achieved CR/PR of any duration/stable disease for ≥ 6 months; resistant-without CR/PR/SD < 6 months) were enrolled to receive MLN0128+exemestane/fulvestrant.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane

Arm description:

Sapanisertib 5 mg, unmilled active pharmaceutical ingredient (API) capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles).

Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sapanisertib capsules

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane coated tablets

Arm title	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant
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Arm description:

Sapanisertib 5 mg, unmilled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection, intramuscularly (IM), once on Day 1 of each cycle (Up to 57 cycles).

Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sapanisertib capsules

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: Fulvestrant Intramuscular (IM) injection	
Arm title	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane
Arm description: Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 8 cycles).	
Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Sapanisertib capsules	
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details: Exemestane coated tablets	
Arm title	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
Arm description: Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle up to 14 cycles plus fulvestrant 500 mg, injection, IM, once on Day 1 of each cycle (Up to 14 cycles).	
Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Sapanisertib capsules	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: Fulvestrant Intramuscular (IM) injection	
Arm title	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane
Arm description: Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 18 cycles).	
Arm type	Experimental

Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Sapanisertib capsules	
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Exemestane coated tablets	
Arm title	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)
Arm description:	
Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 14 cycles) in everolimus sensitive participants.	
Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Sapanisertib capsules	
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Exemestane coated tablets	
Arm title	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive)
Arm description:	
Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 17 cycles) in everolimus sensitive participants.	
Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Sapanisertib capsules	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant Intramuscular (IM) injection

Arm title	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)
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Arm description:

Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles) in everolimus resistant participants.

Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sapanisertib capsules

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane coated tablets

Arm title	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant)
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Arm description:

Sapanisertib 4 mg, milled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 9 cycles) in everolimus resistant participants.

Arm type	Experimental
Investigational medicinal product name	Sapanisertib
Investigational medicinal product code	
Other name	MLN0128
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sapanisertib capsules

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant Intramuscular (IM) injection

Number of subjects in period 1	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane
Started	6	6	3
Completed	0	0	0
Not completed	6	6	3
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
Adverse event, non-fatal	1	1	1
Progressive Disease	5	4	2
Study Terminated by Sponsor	-	1	-

Number of subjects in period 1	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)
Started	3	6	43
Completed	0	0	0
Not completed	3	6	43
Consent withdrawn by subject	1	-	2
Physician decision	-	-	1
Adverse event, non-fatal	-	-	5
Progressive Disease	2	6	35
Study Terminated by Sponsor	-	-	-

Number of subjects in period 1	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant)
Started	8	35	8
Completed	0	0	0
Not completed	8	35	8
Consent withdrawn by subject	-	3	1
Physician decision	-	-	-
Adverse event, non-fatal	-	6	1
Progressive Disease	7	26	6
Study Terminated by Sponsor	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description:

All enrolled participants

Reporting group values	Overall Study	Total	
Number of subjects	118	118	
Age categorical			
Units: Subjects			
Adults (18-64 years)	83	83	
From 65-84 years	35	35	
Age Continuous			
Units: years			
arithmetic mean	57.31		
full range (min-max)	32 to 83	-	
Sex: Female, Male			
9999 = Data for this arm group is available in subject analysis set 'Phase 1 (Part 2): Sapanisertib 3 mg QD+Exemestane/Fulvestrant'.			
Units: Subjects			
Female	118	118	
Male	0	0	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	103	103	
Unknown or Not Reported	11	11	
Race/Ethnicity, Customized			
Units: Subjects			
White	98	98	
Not Reported	6	6	
Black or African American	7	7	
Asian	4	4	
Other	3	3	
Region of Enrollment			
Units: Subjects			
United States	95	95	
Belgium	16	16	
France	7	7	
Height			
Number analyzed is the number of participants with data available for height.			
Units: cm			
arithmetic mean	165.02		
full range (min-max)	150 to 183	-	
Weight			
Number analyzed is the number of participants with data available for weight.			
Units: kg			
arithmetic mean	70.37		

full range (min-max)	46.5 to 139	-	
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End points

End points reporting groups

Reporting group title	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane
Reporting group description: Sapanisertib 5 mg, unmilled active pharmaceutical ingredient (API) capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles).	
Reporting group title	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant
Reporting group description: Sapanisertib 5 mg, unmilled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection, intramuscularly (IM), once on Day 1 of each cycle (Up to 57 cycles).	
Reporting group title	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane
Reporting group description: Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 8 cycles).	
Reporting group title	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
Reporting group description: Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle up to 14 cycles plus fulvestrant 500 mg, injection, IM, once on Day 1 of each cycle (Up to 14 cycles).	
Reporting group title	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane
Reporting group description: Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 18 cycles).	
Reporting group title	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)
Reporting group description: Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 14 cycles) in everolimus sensitive participants.	
Reporting group title	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive)
Reporting group description: Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 17 cycles) in everolimus sensitive participants.	
Reporting group title	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)
Reporting group description: Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles) in everolimus resistant participants.	
Reporting group title	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant)
Reporting group description: Sapanisertib 4 mg, milled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 9 cycles) in everolimus resistant participants.	

Primary: Phase 1: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Phase 1: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) ^{[1][2]}
End point description: An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of	

each AE to study drug will be determined by the Investigator. Safety Population included participants who received at least 1 dose of any study drug.

End point type	Primary
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End point timeframe:

First dose of study drug through 30 days after the last dose (Up to 52 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was performed in Phase 1 of the study.

[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: This endpoint was performed in Phase 1 of the study.

End point values	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	3	3
Units: participants				
Any AE	6	6	3	3
SAEs	1	2	0	0

End point values	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: participants				
Any AE	6			
SAEs	2			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Clinical Benefit Rate at 16 Weeks (CBR-16)

End point title	Phase 2: Clinical Benefit Rate at 16 Weeks (CBR-16) ^{[3][4]}
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End point description:

CBR-16 was defined as the percentage of participants who achieved confirmed complete response (CR) or partial response (PR) of any duration or had confirmed stable disease (SD) as best response and the first 2 or more post baseline scans had PR/SD and the duration of SD was >112 days. Disease response was assessed for target lesions by computed tomography (CT) or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines. CR is disappearance of all target lesions. PR is $\geq 30\%$ decrease in the sum of the longest diameter of target lesions. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression (PD). Response-Evaluable Population included participants who received at least 1 dose of study drug and had measurable disease at baseline.

End point type	Primary
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End point timeframe:

Week 16

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was performed in Phase 2 of the study.

[4] - 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: This endpoint was performed in Phase 2 of the study.

End point values	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Resistant)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	8	35	8
Units: percentage of participants				
number (confidence interval 95%)	44 (29.1 to 60.1)	50 (15.7 to 84.3)	23 (10.4 to 40.1)	25 (3.2 to 65.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Clinical Benefit Rate at 24 Weeks (CBR-24)

End point title	Phase 2: Clinical Benefit Rate at 24 Weeks (CBR-24) ^[5]
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End point description:

CBR-24 was defined as the percentage of participants who achieved confirmed CR or PR at any time or had confirmed SD as best response and the first 2 or more post baseline scans had PR/SD and the duration of stable disease was >168 days. Disease response was assessed for target lesions by CT or MRI according to RECIST version 1.1 guidelines. CR is disappearance of all target lesions. PR is ≥30% decrease in the sum of the longest diameter of target lesions. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Response-Evaluable Population included participants who received at least 1 dose of study drug and had measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Week 24

Notes:

[5] - 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: This endpoint was performed in Phase 2 of the study.

End point values	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Resistant)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	8	35	8
Units: percentage of participants				
number (confidence interval 95%)	28 (15.3 to 43.7)	38 (8.5 to 75.5)	23 (10.4 to 40.1)	25 (3.2 to 65.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Response Rate (ORR)

End point title	Phase 2: Overall Response Rate (ORR) ^[6]
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End point description:

ORR is defined as the percentage of participants with confirmed CR or PR as per RECIST version 1.1 guidelines. CR is disappearance of all target lesions. PR is $\geq 30\%$ decrease in the sum of the longest diameter of target lesions. Response-Evaluable Population included participants who received at least 1 dose of study drug and had measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Baseline then every 2 cycles from Cycles 2 through 6, and every 3 cycles thereafter in a 28-day cycle up to End of Treatment (EOT) (Up to 24 months)

Notes:

[6] - 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: This endpoint was performed in Phase 2 of the study.

End point values	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg + Fulvestrant (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg + Fulvestrant (Everolimus Resistant)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	8	35	8
Units: percentage of participants				
number (confidence interval 95%)	7 (1.5 to 19.1)	13 (1 to 52.7)	0 (0 to 0)	13 (1 to 52.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-Free Survival (PFS)

End point title	Phase 2: Progression-Free Survival (PFS) ^[7]
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End point description:

PFS is defined as the time in months from the date of first dose of study treatment to the date of the first documented disease progression or death. Disease progression was defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; or the appearance of one or more new lesions. Safety Population included participants who received at least 1 dose of study drug. For a participant whose disease had not progressed and was last known to be alive, PFS was censored at the last response assessment that was stable disease or better. 99999: Upper limit of Confidence Interval (CI) was not reached due to low number of participants with events.

End point type	Secondary
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End point timeframe:

Baseline then every 2 cycles from Cycles 2 through 6, and every 3 cycles thereafter in a 28-day cycle, then every 3 months after EOT until disease progression or death (Up to 24 months)

Notes:

[7] - 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: This endpoint was performed in Phase 2 of the study.

End point values	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Resistant)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	8	35	8
Units: months				
median (confidence interval 95%)	4.1 (1.9 to 5.5)	5.5 (1.8 to 99999)	3.3 (1.9 to 3.7)	5.4 (1.7 to 8.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS) ^[8]
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End point description:

OS is the time in months from start of study treatment to date of death due to any cause. Data for the analysis of OS included the censored data at the timepoint that the participant was last known to be alive. Safety Population included participants who received at least 1 dose of study drug. Participants without documentation of death at the time of analysis were censored at the date last known to be alive.

End point type	Secondary
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End point timeframe:

Up to 24 months

Notes:

[8] - 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: This endpoint was performed in Phase 2 of the study.

End point values	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Resistant)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	8	35	8
Units: months				
median (confidence interval 95%)	15.9 (14.1 to 19.5)	20.7 (8.6 to 20.7)	14.0 (10.6 to 16.0)	13.0 (4.1 to 21.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Best Percent Change from Baseline in Tumor Size

End point title | Phase 2: Best Percent Change from Baseline in Tumor Size^[9]

End point description:

Participants from Safety Population included participants who received at least 1 dose of study drug and provided both baseline and at least one post-baseline disease response.

End point type | Secondary

End point timeframe:

Baseline to Month 24

Notes:

[9] - 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: This endpoint was performed in Phase 2 of the study.

End point values	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg+Fulvestran t (Everolimus Resistant)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	7	27	7
Units: percentage change in tumor size				
arithmetic mean (standard deviation)	-0.46 (± 34.89)	0.96 (± 38.98)	1.76 (± 31.14)	-18.91 (± 19.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase1: Cmax: Maximum Observed Plasma Concentration for Sapanisertib

End point title | Phase1: Cmax: Maximum Observed Plasma Concentration for Sapanisertib^[10]

End point description:

Pharmacokinetic (PK) Population included participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15. n= number analyzed is the number of participants with data available for analyses at the given timepoint.

End point type | Secondary

End point timeframe:

Cycle 1 Day 15 and Cycle 2 Day 1 pre-dose and multiple timepoints (Up to 8 hours) post-dose

Notes:

[10] - 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: This endpoint was performed in Phase 1 of the study.

End point values	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	3	3
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 15 (n=6,0,3,2,6)	57.72 (± 9.927)	9999 (± 9999)	47.40 (± 6.583)	50.90 (± 23.476)
Cycle 2 Day 1 (n=5,5,3,3,5)	38.68 (± 20.551)	44.96 (± 34.459)	43.47 (± 0.874)	45.30 (± 16.235)

End point values	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 15 (n=6,0,3,2,6)	45.37 (± 9.644)			
Cycle 2 Day 1 (n=5,5,3,3,5)	44.68 (± 8.636)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Sapanisertib

End point title	Phase 1: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Sapanisertib ^[11]
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End point description:

PK Population included participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15. n=number analyzed is the number of participants with data available for analyses at the given timepoint.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 15 and Cycle 2 Day 1 pre-dose and multiple timepoints (Up to 8 hours) post-dose

Notes:

[11] - 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: This endpoint was performed in Phase 1 of the study.

End point values	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	3	3
Units: hour				
median (full range (min-max))				
Cycle 1 Day 15 (n=6,0,3,2,6)	3.005 (0.58 to 7.30)	9999 (9999 to 9999)	0.600 (0.45 to 1.00)	1.035 (1.00 to 1.07)
Cycle 2 Day 1 (n=5,5,3,3,5)	2.280 (0.85 to 3.58)	3.500 (0.92 to 4.03)	0.980 (0.68 to 1.00)	1.000 (0.48 to 1.12)

End point values	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hour				
median (full range (min-max))				
Cycle 1 Day 15 (n=6,0,3,2,6)	2.000 (0.50 to 3.55)			
Cycle 2 Day 1 (n=5,5,3,3,5)	2.000 (0.50 to 3.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: AUC(0-24): Area under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours, Calculated using the Observed Value of the Last Quantifiable Concentration Over the Dosing Interval for Sapanisertib

End point title	Phase 1: AUC(0-24): Area under the Plasma Concentration-time Curve from Time 0 to Time 24 Hours, Calculated using the Observed Value of the Last Quantifiable Concentration Over the Dosing Interval for Sapanisertib ^[12]
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End point description:

AUC(0-24) is the area under the plasma concentration-time curve of the samples collected up to 8 hours and extrapolated up to 24 hours. Participants from PK Population included participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15. Number analyzed is the number of participants with data available for analyses at the given timepoint.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 15 pre-dose and multiple timepoints (Up to 8 hours) post-dose, extrapolated to 24 hours post-dose

Notes:

[12] - 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: This endpoint was performed in Phase 1 of the study.

End point values	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	0 ^[13]	3	2
Units: h*ng/mL				
arithmetic mean (standard deviation)	577.081 (± 331.9813)	()	178.063 (± 46.1416)	332.618 (± 228.5641)

Notes:

[13] - PK data was not available at Cycle 1 Day 15.

End point values	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: h*ng/mL				
arithmetic mean (standard deviation)	277.626 (± 64.0661)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: AUC(0-last): Area under the Plasma Concentration-time Curve from Time 0 to Time tau Over the Dosing Interval for MLN0128

End point title	Phase 1: AUC(0-last): Area under the Plasma Concentration-time Curve from Time 0 to Time tau Over the Dosing Interval for MLN0128 ^[14]
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End point description:

AUC(0-last) is the area under the plasma concentration-time curve of the samples collected up to 8 hours and extrapolated up to last time point. PK Population included participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15. n=number analyzed is the number of participants with data available for analyses at the given timepoint.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 15 pre-dose and multiple timepoints (Up to 8 hours) post-dose, extrapolated to last timepoint

Notes:

[14] - 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: This endpoint was performed in Phase 1 of the study.

End point values	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	5	3	3
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 15 (n=6,0,3,2,6)	577.081 (± 331.9813)	9999 (± 9999)	164.123 (± 52.6287)	332.618 (± 228.5641)
Cycle 1 Day 2 (n=5,5,3,3,5)	101.599 (± 51.0248)	109.496 (± 82.3968)	89.576 (± 15.0117)	109.548 (± 52.8500)

End point values	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 15 (n=6,0,3,2,6)	251.165 (± 83.7121)			
Cycle 1 Day 2 (n=5,5,3,3,5)	116.557 (± 8.6059)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Terminal Elimination Half-life (T1/2) for Sapanisertib

End point title	Phase 1: Terminal Elimination Half-life (T1/2) for
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End point description:

Participants from PK Population, participants with sufficient dosing and PK data to reliably estimate PK parameters. PK data was not available for Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant arm group at Cycle 1 Day 15.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 15 pre-dose and multiple timepoints (Up to 8 hours) post-dose

Notes:

[15] - 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: This endpoint was performed in Phase 1 of the study.

End point values	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0 ^[16]	3	2
Units: hour				
arithmetic mean (standard deviation)	6.639 (± 1.2176)	()	3.161 (± 1.6585)	7.777 (± 2.9177)

Notes:

[16] - PK data was not available at Cycle 1 Day 15.

End point values	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: hour				
arithmetic mean (standard deviation)	5.370 (± 1.4638)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose up to 30 days post last dose of study drug (Up to 52 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane
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Reporting group description:

Sapanisertib 5 mg, unmilled active pharmaceutical ingredient (API) capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 12 cycles).

Reporting group title	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant
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Reporting group description:

Sapanisertib 5 mg, unmilled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection, intramuscularly (IM), once on Day 1 of each cycle (Up to 57 cycles).

Reporting group title	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane
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Reporting group description:

Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 8 cycles).

Reporting group title	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant
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Reporting group description:

Sapanisertib 3 mg, milled API capsule, once daily in a 28-day cycle up to 14 cycles plus fulvestrant 500 mg, injection, IM, once on Day 1 of each cycle (Up to 14 cycles).

Reporting group title	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane
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Reporting group description:

Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 18 cycles).

Reporting group title	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)
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Reporting group description:

Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus exemestane 25 mg, tablets, once daily in a 28-day cycle (Up to 14 cycles) in everolimus sensitive participants.

Reporting group title	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)
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Reporting group description:

Sapanisertib 4 mg, milled API capsule, once daily, in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 12 cycles) in everolimus resistant participants.

Reporting group title	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive)
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Reporting group description:

Sapanisertib 4 mg, milled API capsule once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 17 cycles) in everolimus sensitive participants.

Reporting group title	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant)
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Reporting group description:

Sapanisertib 4 mg, milled API capsule, once daily in a 28-day cycle plus fulvestrant 500 mg, injection IM, once on Day 1 of each cycle (Up to 9 cycles) in everolimus resistant participants.

Serious adverse events	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (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
Investigations			
Clostridium test positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (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
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (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
Sepsis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Appendicitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Failure to thrive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	2 / 6 (33.33%)	11 / 43 (25.58%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
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			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (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
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Clostridium test positive			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 35 (14.29%)	3 / 8 (37.50%)	2 / 8 (25.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (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
Cancer pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (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
Metastases to bone			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Clostridium test positive			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (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			
Alcohol poisoning			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (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
Syncope			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (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			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (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
Vomiting			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (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
Breast cellulitis			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Phase 1 (Part 1): Sapanisertib 5 mg + Exemestane	Phase 1 (Part 1): Sapanisertib 5 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 3 mg + Exemestane
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Hypotension			

subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis limb			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 6 (66.67%)	6 / 6 (100.00%)	1 / 3 (33.33%)
occurrences (all)	7	6	1
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Injection site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal dryness			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Genital rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	0 / 3 (0.00%)
occurrences (all)	1	4	0
Cough			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hypoxia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Atelectasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pleurisy			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiration abnormal			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dysphoria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Stress			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hallucinations, mixed			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Initial insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Panic attack			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Product issues			
Thrombosis in device			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Investigations			
Weight decreased			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Amylase decreased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood albumin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood calcium increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood sodium decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
International normalised ratio decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Protein total increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Protein urine			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Transaminases increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Injury, poisoning and procedural complications			
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	1 / 3 (33.33%) 1
Humerus fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 3 (33.33%) 1
Rib fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Animal bite subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Procedural nausea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Spinal compression fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Thoracic vertebral fracture			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tachyarrhythmia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	4	1	0
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Ataxia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hyperaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Serotonin syndrome			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
VIth nerve paralysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Cognitive disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ageusia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dystonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoglossal nerve disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sciatica			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eosinophilia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Diplopia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Retinal scar			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 6 (50.00%)	5 / 6 (83.33%)	2 / 3 (66.67%)
occurrences (all)	5	11	2
Nausea			
subjects affected / exposed	6 / 6 (100.00%)	4 / 6 (66.67%)	1 / 3 (33.33%)
occurrences (all)	7	5	1
Stomatitis			

subjects affected / exposed	5 / 6 (83.33%)	3 / 6 (50.00%)	0 / 3 (0.00%)
occurrences (all)	10	5	0
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 3 (33.33%)
occurrences (all)	1	2	2
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Dyspepsia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 3 (100.00%)
occurrences (all)	2	1	3
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Glossodynia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	1 / 3 (33.33%)
occurrences (all)	4	3	1
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	8	1	1
Rash pruritic			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0

Rash macular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Acne			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ingrowing nail			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pruritus generalised			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Psoriasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rash papular			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nail ridging			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Onychoclasia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eczema			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oliguria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Azotaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Leukocyturia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Micturition urgency subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Endocrine disorders Thyroid disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	1 / 6 (16.67%) 2	2 / 3 (66.67%) 2
Pain in extremity subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2	1 / 3 (33.33%) 1
Joint swelling subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Back pain			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Muscle fatigue			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Osteopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pain in jaw			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint range of motion decreased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscle twitching			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pathological fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Synovial cyst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tenosynovitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Oral candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Arthritis infective			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Catheter site infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hepatic infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Rash pustular subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Spingomonas paucimobilis infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Streptococcal infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	3 / 6 (50.00%) 4	1 / 3 (33.33%) 1
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3	4 / 6 (66.67%) 5	0 / 3 (0.00%) 0
Dehydration subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0
Hypercholesterolaemia			

subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hypercalcaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hyperlipidaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Hyponatraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Lactic acidosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Food intolerance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypermagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase 1 (Part 2): Sapanisertib 3 mg + Fulvestrant	Phase 1 (Part 2): Sapanisertib 4 mg + Exemestane	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Sensitive)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	6 / 6 (100.00%)	43 / 43 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Tumour pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	3
Hypotension			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	7
Flushing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Venous thrombosis limb			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 3 (100.00%)	4 / 6 (66.67%)	19 / 43 (44.19%)
occurrences (all)	3	4	30
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Injection site pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Injection site rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	5
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	4
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	3
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	5
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Vulvovaginal dryness			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	3
Genital rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Pelvic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	8 / 43 (18.60%)
occurrences (all)	0	1	11
Cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	7 / 43 (16.28%)
occurrences (all)	0	1	9
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	2 / 43 (4.65%)
occurrences (all)	0	1	2
Atelectasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Pleurisy			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Sleep apnoea syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Nasal dryness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Pleuritic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Respiration abnormal			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	3 / 43 (6.98%)
occurrences (all)	0	1	3
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	3
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dysphoria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Stress			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Irritability			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hallucinations, mixed			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Initial insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Panic attack			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Product issues			
Thrombosis in device			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	1 / 3 (33.33%)	3 / 6 (50.00%)	6 / 43 (13.95%)
occurrences (all)	2	3	8
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	6 / 43 (13.95%)
occurrences (all)	0	0	8
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Amylase increased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 6 (16.67%)	1 / 43 (2.33%)
occurrences (all)	1	1	1
Blood creatinine increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	1	0	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	4 / 43 (9.30%)
occurrences (all)	0	1	4
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	4 / 43 (9.30%)
occurrences (all)	0	0	5
Blood cholesterol increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	3 / 43 (6.98%)
occurrences (all)	0	1	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	1	0	3
International normalised ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
White blood cells urine positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	4 / 43 (9.30%)
occurrences (all)	0	0	9
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	4 / 43 (9.30%)
occurrences (all)	0	0	6
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	4 / 43 (9.30%)
occurrences (all)	0	0	5
Blood phosphorus increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Blood phosphorus decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Blood triglycerides increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Amylase decreased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Blood calcium increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	2
Blood glucose increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Blood sodium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
International normalised ratio decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Protein total increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Protein urine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Transaminases increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Injury, poisoning and procedural complications			
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Humerus fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Rib fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 6 (16.67%) 1	0 / 43 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Animal bite subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Procedural nausea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Procedural pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Spinal compression fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Thoracic vertebral fracture			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Tachyarrhythmia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	8 / 43 (18.60%)
occurrences (all)	0	0	9
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	7 / 43 (16.28%)
occurrences (all)	0	1	11
Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	11 / 43 (25.58%)
occurrences (all)	0	1	13
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	5 / 43 (11.63%)
occurrences (all)	0	1	6
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Ataxia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Serotonin syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
With nerve paralysis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Ageusia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dystonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hypoglossal nerve disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Sciatica			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	6 / 43 (13.95%)
occurrences (all)	0	1	8
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Eosinophilia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Eye disorders			

Cataract			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	3
Eye pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	2
Visual impairment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Vitreous floaters			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Conjunctival haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Retinal scar			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	4 / 6 (66.67%)	17 / 43 (39.53%)
occurrences (all)	4	5	27
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	3 / 6 (50.00%)	23 / 43 (53.49%)
occurrences (all)	2	5	29
Stomatitis			

subjects affected / exposed	0 / 3 (0.00%)	2 / 6 (33.33%)	10 / 43 (23.26%)
occurrences (all)	0	3	11
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	3 / 6 (50.00%)	10 / 43 (23.26%)
occurrences (all)	0	4	13
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	1 / 6 (16.67%)	6 / 43 (13.95%)
occurrences (all)	1	1	7
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	5 / 43 (11.63%)
occurrences (all)	0	1	5
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	4 / 43 (9.30%)
occurrences (all)	0	0	4
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	2 / 43 (4.65%)
occurrences (all)	0	1	2
Flatulence			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	3
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Gingival pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			

subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	7 / 43 (16.28%)
occurrences (all)	0	0	7
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Abdominal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Eructation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Gastrointestinal disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 3 (100.00%)	3 / 6 (50.00%)	11 / 43 (25.58%)
occurrences (all)	4	3	14
Rash maculo-papular			
subjects affected / exposed	1 / 3 (33.33%)	2 / 6 (33.33%)	5 / 43 (11.63%)
occurrences (all)	1	6	6
Rash pruritic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1

Rash macular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Acne			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	1	0	4
Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	4 / 43 (9.30%)
occurrences (all)	1	0	5
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Ingrowing nail			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pruritus generalised			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Psoriasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Rash papular			

subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Skin exfoliation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Skin irritation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	3
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Nail ridging			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Onychoclasia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Decubitus ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Eczema			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Oliguria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Azotaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 2
Leukocyturia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Micturition urgency subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Endocrine disorders Thyroid disorder subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	3 / 43 (6.98%) 3
Pain in extremity subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 6 (16.67%) 1	2 / 43 (4.65%) 2
Joint swelling subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 6 (16.67%) 1	0 / 43 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	3 / 43 (6.98%) 3
Back pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	8 / 43 (18.60%)
occurrences (all)	0	0	12
Muscle fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	3 / 43 (6.98%)
occurrences (all)	0	1	3
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Osteonecrosis of jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	6 / 43 (13.95%)
occurrences (all)	0	0	6
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	2
Bursitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Joint range of motion decreased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Joint stiffness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Muscle twitching			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Pathological fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Synovial cyst			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Tenosynovitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	7 / 43 (16.28%)
occurrences (all)	0	1	8
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1

Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Arthritis infective			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Catheter site infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Fungal skin infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hepatic infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1

Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Rash pustular subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 3
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Spingomonas paucimobilis infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Streptococcal infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	1 / 43 (2.33%) 1
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	0 / 43 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 2	1 / 6 (16.67%) 1	16 / 43 (37.21%) 19
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 6 (16.67%) 2	11 / 43 (25.58%) 25
Dehydration subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 6 (0.00%) 0	3 / 43 (6.98%) 3
Hypercholesterolaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	7 / 43 (16.28%)
occurrences (all)	0	1	8
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hyperlipidaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Lactic acidosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Hypertriglyceridaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	4
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	2
Hypernatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Hyperuricaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Food intolerance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hypermagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Phase 2: Sapanisertib 4 mg + Exemestane (Everolimus Resistant)	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Sensitive)	Phase 2: Sapanisertib 4 mg+Fulvestrant (Everolimus Resistant)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 35 (100.00%)	8 / 8 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypotension			

subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	4 / 35 (11.43%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	5	0	0
Flushing			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Lymphoedema			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis limb			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 35 (45.71%)	6 / 8 (75.00%)	2 / 8 (25.00%)
occurrences (all)	16	6	2
Pyrexia			
subjects affected / exposed	3 / 35 (8.57%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Injection site pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injection site rash			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Asthenia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	1 / 8 (12.50%) 1	2 / 8 (25.00%) 2
Chest pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Gait disturbance subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
General physical health deterioration subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Immune system disorders Contrast media allergy subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Vulvovaginal dryness			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Genital rash			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 35 (5.71%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
Cough			
subjects affected / exposed	4 / 35 (11.43%)	3 / 8 (37.50%)	2 / 8 (25.00%)
occurrences (all)	4	4	2
Hypoxia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Atelectasis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Pleural effusion			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pleurisy			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Sinus congestion			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Upper-airway cough syndrome			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Respiration abnormal			

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 2	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 35 (8.57%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	4	1	0
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Dysphoria			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Stress			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Irritability			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Hallucination			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hallucinations, mixed			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Initial insomnia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Panic attack			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

Product issues			
Thrombosis in device			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	4 / 35 (11.43%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	5	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 35 (14.29%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	6	0	2
Alanine aminotransferase increased			
subjects affected / exposed	4 / 35 (11.43%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	5	0	3
Amylase increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	1
Blood creatinine increased			
subjects affected / exposed	6 / 35 (17.14%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	7	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	2
Blood cholesterol increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
International normalised ratio increased			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
White blood cells urine positive			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	2
White blood cell count decreased			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Neutrophil count decreased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood phosphorus increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Amylase decreased			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood albumin decreased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood calcium increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	4	0	0
Blood potassium increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood sodium decreased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
International normalised ratio decreased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Low density lipoprotein increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Protein total increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Protein urine			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

Transaminases increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Injury, poisoning and procedural complications			
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Humerus fracture subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Rib fracture subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Animal bite subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Fall subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0
Fracture subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Procedural nausea subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Spinal compression fracture subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Thoracic vertebral fracture			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tachyarrhythmia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 35 (11.43%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	4	0	0
Dizziness			
subjects affected / exposed	3 / 35 (8.57%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	3	3	0
Headache			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Paraesthesia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ataxia			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Serotonin syndrome			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
With nerve paralysis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ageusia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Dystonia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypoglossal nerve disorder			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Sciatica			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 35 (17.14%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	8	0	2
Leukocytosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 8 (25.00%)	1 / 8 (12.50%)
occurrences (all)	2	2	1
Eosinophilia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Visual impairment			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Retinal scar			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 35 (25.71%)	3 / 8 (37.50%)	6 / 8 (75.00%)
occurrences (all)	10	3	9
Nausea			
subjects affected / exposed	15 / 35 (42.86%)	7 / 8 (87.50%)	4 / 8 (50.00%)
occurrences (all)	21	8	5
Stomatitis			

subjects affected / exposed	8 / 35 (22.86%)	3 / 8 (37.50%)	2 / 8 (25.00%)
occurrences (all)	11	3	2
Vomiting			
subjects affected / exposed	10 / 35 (28.57%)	1 / 8 (12.50%)	5 / 8 (62.50%)
occurrences (all)	13	2	7
Constipation			
subjects affected / exposed	5 / 35 (14.29%)	1 / 8 (12.50%)	2 / 8 (25.00%)
occurrences (all)	5	1	2
Abdominal pain			
subjects affected / exposed	2 / 35 (5.71%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Toothache			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Dyspepsia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Gingival pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			

subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	3 / 35 (8.57%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Abdominal discomfort			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Colitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Lip dry			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 35 (17.14%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	8	1	1
Rash maculo-papular			
subjects affected / exposed	3 / 35 (8.57%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	3	1	0
Rash pruritic			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	4 / 35 (11.43%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	5	0	0

Rash macular			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Dermatitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Ingrowing nail			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pruritus generalised			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Psoriasis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash papular			

subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Skin exfoliation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Nail ridging			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Onychoclasia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Decubitus ulcer			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Eczema			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Acute kidney injury			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Haematuria			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Oliguria			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Azotaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Leukocyturia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Micturition urgency subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Endocrine disorders Thyroid disorder subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	2 / 8 (25.00%) 2	1 / 8 (12.50%) 1
Pain in extremity subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Joint swelling subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	2 / 8 (25.00%) 2
Back pain			

subjects affected / exposed	4 / 35 (11.43%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	5	0	2
Muscle fatigue			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Osteonecrosis of jaw			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Osteopenia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Muscular weakness			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Bursitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Joint range of motion decreased			

subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Muscle twitching			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pathological fracture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Synovial cyst			
subjects affected / exposed	0 / 35 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Tenosynovitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 35 (14.29%)	3 / 8 (37.50%)	1 / 8 (12.50%)
occurrences (all)	5	3	1
Rhinitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Oral candidiasis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Arthritis infective			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Bacteraemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Bacterial infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Catheter site infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Diverticulitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hepatic infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1
Rash pustular subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Spingomonas paucimobilis infection subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Streptococcal infection subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	9 / 35 (25.71%) 10	1 / 8 (12.50%) 1	2 / 8 (25.00%) 2
Hyperglycaemia subjects affected / exposed occurrences (all)	16 / 35 (45.71%) 29	0 / 8 (0.00%) 0	4 / 8 (50.00%) 8
Dehydration subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Hypercholesterolaemia			

subjects affected / exposed	3 / 35 (8.57%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	3	1	1
Hypokalaemia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Hypophosphataemia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Hypercalcaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	3 / 35 (8.57%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	4	0	0
Lactic acidosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	3 / 35 (8.57%)	0 / 8 (0.00%)	3 / 8 (37.50%)
occurrences (all)	3	0	3
Hypertriglyceridaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Hyperkalaemia			
subjects affected / exposed	3 / 35 (8.57%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Hypernatraemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			

subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 8 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	3
Food intolerance			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypermagnesaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 35 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2014	<ul style="list-style-type: none">• The primary purpose of this amendment was to expand the number of investigative sites to include sites in the US, Belgium, and France. In conjunction with this expansion, the sponsor agreed to provide exemestane and fulvestrant to sites outside of the US, and references to the Summary of Product Characteristics (SmPC) for each agent were added.• This amendment also incorporated procedural clarifications contained in prior administrative letters and clarified posttreatment follow-up procedures, including a specification for an overall study ending timepoint no later than 6 months after the last patient completed the end of treatment (EOT) visit.• To optimize analysis of the phase 2 exploratory endpoint of changes in tumor volume, collection of the most recent prebaseline computed tomography (CT) scan (if available) was added to the screening procedures; availability of the historical prebaseline scan was not a prerequisite for study eligibility.• Several eligibility criteria were clarified: the inclusion criterion for HER2-status was simplified to reference the updated ASCO/CAP testing criteria, and the exclusion criterion for treatment with cytochrome P450 (CYP) inhibitors was aligned with prohibited concomitant medications.
15 September 2014	<ul style="list-style-type: none">• The primary purpose of Amendment 2 was to evaluate the safety, tolerability, and pharmacokinetic (PK) of a new sapanisertib capsule based on milled API before initiation of the phase 2 portion of the study. The new capsules based on milled API were to be taken on an empty stomach.
12 March 2015	<ul style="list-style-type: none">• The primary purpose of Amendment 3 was to clarify that enrolled patients in France or Belgium would not have had prior combination therapy with fulvestrant and everolimus and would not receive this combination in the study. Additionally, this amendment clarified the timing of sapanisertib and exemestane administration to allow for exemestane to be administered after a meal in accordance with the product label. A guide for managing patients with noninfectious pneumonitis was added, and the vendor and contact information to report product complaints was updated.
22 October 2015	<ul style="list-style-type: none">• The primary purpose of Amendment 4 was to modify the eligibility criteria to expand the pool of potential study participants and clarify disease status confirmation requirements, and to decrease the number of PK samples required in phase 2. This amendment also revised the excluded medications section of the protocol based on characterization of PK from the phase 1 portion of this study and other clinical studies in the sapanisertib development program. The starting dose for the phase 2 portion of this study was confirmed as 4 mg (milled) sapanisertib + either exemestane 25 mg or fulvestrant 500 mg, based on a safety and tolerability review of patients in cohort 2 of phase 1b part 2. It was not anticipated that these modifications would affect the scientific integrity of the study or the safety of study participants. Administrative changes were also made, such as introducing the new compound code for the study drug, adding the suspected unexpected serious adverse reactions (SUSAR) language, and• revising the product complaints vendor and contact information.
12 May 2017	<ul style="list-style-type: none">• The primary purpose of Amendment 5 was to allow the use of ondansetron and granisetron for antiemetic therapy and prophylaxis, update the definition of the response-evaluable population, and remove the PK/tumor-pharmacodynamic cohort.

26 October 2017	<ul style="list-style-type: none"> The primary purpose of Amendment 6 was to update sections affected by new nonclinical data for sapanisertib metabolism by specific cytochrome P450 (CYP) isoforms. Exclusion criteria, the list of prohibited concomitant medications and CYP inhibitors, dietary restrictions related to CYP inhibitors and inducers, the use of contrast with MRI, and the description of potential DDIs were updated accordingly.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported