Clinical trial results:
A phase Ib trial of LEE011 in combination with everolimus (RAD001) and exemestane in the treatment of postmenopausal women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer

Summary

EudraCT number	2012-005461-13
Trial protocol	ES DE IT GB FR
Global end of trial date	16 April 2020

Results information

Result version number	v1 (current)
This version publication date	22 April 2021
First version publication date	22 April 2021

Trial information

Trial identification

Sponsor protocol code	CLEE011X2106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01857193
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	16 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Dose escalation:
- To estimate the maximum tolerated dose (MTD(s)) and/or recommended Phase 2 dose (RP2D) of LEE011 (ribociclib) in combination with everolimus and exemestane in patients with estrogen receptor-positive (ER-positive) human epidermal growth factor receptor 2-negative (HER2-negative) advanced breast cancer.*

Expansion:
- To characterize the safety and tolerability of the triplet combination of LEE011 (ribociclib) + everolimus + exemestane in patients naive or refractory to cyclin-dependent kinase 4/6 (CDK4/6) inhibitor based therapy.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2013
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	Belgium: 5
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United States: 97
Worldwide total number of subjects	132
EEA total number of subjects	31

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)	98
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 13 centers across 5 countries: USA (8), Spain (2), France (1), Belgium (1), Hong Kong (1)

Pre-assignment

Screening details:

Participants were divided into two phases: dose escalation and dose expansion. Each phase was further divided into three groups (two triplets and one doublet) depending on the varied dose levels.

Period 1

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

Blinding implementation details:

Not applicable as this was an open-label study

Arms

Are arms mutually exclusive?	Yes
Arm title	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive

Arm description:

Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group

Arm type	Experimental
Investigational medicinal product name	LEE011 (Ribociclib) + Everolimus + Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

ribociclib (200 mg once daily 3 weeks on/1 week off), a reduced dose of everolimus (2.5 mg once daily) and exemestane (25 mg once daily)

Arm title	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory

Arm description:

Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

Arm type	Experimental
Investigational medicinal product name	LEE011 (Ribociclib) + Everolimus + Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

ribociclib (200 mg once daily 3 weeks on/1 week off), a reduced dose of everolimus (2.5 mg once daily) and exemestane (25 mg once daily)

Arm title	LEE011(600 mg)+exe(25 mg) esc refractory

Arm description:

Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

Arm type	Experimental

Investigational medicinal product name	LEE011 (Ribociclib) + Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

ribociclib (600 mg once daily 3 weeks on/1 week off) and exemestane (25 mg once daily)

Arm title	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive

Arm description:

Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group

Arm type	Experimental
Investigational medicinal product name	LEE011 (Ribociclib) + Everolimus + Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

ribociclib (300 mg once daily 3 weeks on/1 week off), a reduced dose of everolimus (2.5 mg once daily) and exemestane (25 mg once daily)

Arm title	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory

Arm description:

Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

Arm type	Experimental
Investigational medicinal product name	LEE011 (Ribociclib) + Everolimus + Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

ribociclib (300 mg once daily 3 weeks on/1 week off), a reduced dose of everolimus (2.5 mg once daily) and exemestane (25 mg once daily)

Arm title	LEE011(600 mg)+exe(25 mg) exp refractory

Arm description:

Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)

Arm type	Experimental
Investigational medicinal product name	LEE011 (Ribociclib) + Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

ribociclib (600 mg once daily 3 weeks on/1 week off) and exemestane (25 mg once daily)

Number of subjects in period 1	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	LEE011(600 mg)+exe(25 mg) esc refractory
Started	41	42	14
Completed	0	0	0
Not completed	41	42	14
Subject withdrew consent	1	3	1
Physician decision	5	9	-
Disease progression	32	26	12
Adverse event, non-fatal	3	3	1
Administrative problems	-	1	-

Number of subjects in period 1	LEE011(300 mg)+eve(2.5 mg)+exe (25mg)	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory
Started	16	17	2
Completed	0	0	0
Not completed	16	17	2
Subject withdrew consent	1	-	-
Physician decision	2	2	-
Disease progression	11	14	1
Adverse event, non-fatal	2	1	1
Administrative problems	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive
Reporting group description:	
Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	
Reporting group title	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory
Reporting group description:	
Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	
Reporting group title	LEE011(600 mg)+exe(25 mg) esc refractory
Reporting group description:	
Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	
Reporting group title	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive
Reporting group description:	
Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	
Reporting group title	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory
Reporting group description:	
Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	
Reporting group title	LEE011(600 mg)+exe(25 mg) exp refractory
Reporting group description:	
Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)	

Reporting group values	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	LEE011(600 mg)+exe(25 mg) esc refractory
Number of subjects	41	42	14
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	33	9
From 65-84 years	11	9	5
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	57.2	56.6	60.4
standard deviation	± 11.03	± 9.89	± 9.31

Sex: Female, Male Units: Participants			
Female	41	42	14
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	7	4	1
Chinese	3	3	0
Other	28	29	11
Missing	3	6	2

Reporting group values	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory
Number of subjects	16	17	2
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	15	1
From 65-84 years	6	2	1
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	60.6	52.9	64.0
standard deviation	± 6.90	± 11.48	± 11.31
Sex: Female, Male Units: Participants			
Female	16	17	2
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	2	2	0
Chinese	0	0	0
Other	12	15	2
Missing	2	0	0

Reporting group values	Total		
Number of subjects	132		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	98		
From 65-84 years	34		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	132		
Male	0		
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	16		
Chinese	6		
Other	97		
Missing	13		

End points

End points reporting groups

Reporting group title	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive
Reporting group description:	
Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group	
Reporting group title	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory
Reporting group description:	
Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	
Reporting group title	LEE011(600 mg)+exe(25 mg) esc refractory
Reporting group description:	
Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	
Reporting group title	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive
Reporting group description:	
Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group	
Reporting group title	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory
Reporting group description:	
Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group	
Reporting group title	LEE011(600 mg)+exe(25 mg) exp refractory
Reporting group description:	
Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)	
Subject analysis set title	Doublet Escalation: LEE011 (600 mg) exe (25 mg) (Fasting)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Doublet combination of LEE011 (600 mg) + exemestane (25 mg) (Fasting)	
Subject analysis set title	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Triplet combination of LEE011 (200 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fasting)	
Subject analysis set title	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Triplet combination of LEE011 (200 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fed)	
Subject analysis set title	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Triplet combination of LEE011 (250 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fasting)	
Subject analysis set title	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Triplet combination of LEE011 (250 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fed)	
Subject analysis set title	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Triplet combination of LEE011 (300 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fasting)

Subject analysis set title	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Triplet combination of LEE011 (300 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fed)

Subject analysis set title	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Triplet combination of LEE011 (350 mg) + everolimus (RAD001, 1 mg) + exemestane (25 mg) (fasting)

Subject analysis set title	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Triplet combination of LEE011 (350 mg) + everolimus (RAD001, 2.5 mg) + exemestane (25 mg) (fed)

Subject analysis set title	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Triplet combination of LEE011 (200 mg) + everolimus (RAD001, 5 mg) + exemestane (25 mg) (fed)

Subject analysis set title	Triplet Escalation ALL
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Triplet Escalation ALL (FED and fasting)

Primary: Dose Escalation: Incidence of Dose Limiting Toxicity (DLT)

End point title	Dose Escalation: Incidence of Dose Limiting Toxicity (DLT)[1]

End point description:

DLT is defined as treatment-related toxicity (classified according Common Toxicity Criteria for Adverse Events (CTCAE) Version 4) occurring during the first 28 treatment days and meeting specific protocol-predefined criteria.

End point type	Primary

End point timeframe:

28 days from dosing or cycle 1

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: No statistical analyses have been specified for this primary end point.

End point values	Doublet Escalation: LEE011 (600 mg) exe (25 mg) (Fasting)	Triplet Escalation ALL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	70		
Units: Participants				
number (not applicable)	2	7		

Statistical analyses

No statistical analyses for this end point

Primary: Dose Expansion: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Dose Expansion: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)[2][3]

End point description:

Adverse events were collected for approximately 4.5 years for dose expansion including the 30 days safety follow-up period.

End point type	Primary

End point timeframe:

Approximately 4.5 years after FPFV

Notes:

[2] - 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: No statistical analyses have been specified for this primary end point.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this primary end point.

End point values	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	17	2	
Units: Participants				
Adverse Events (AEs)	16	17	2	
Serious Adverse Events (SAEs)	4	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Dose Escalation: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)[4]

End point description:

Adverse events were collected for approximately 6.5 years for dose escalation including the 30 days safety follow-up period.

End point type	Secondary

End point timeframe:

Approximately 6.5 years after FPFV

Notes:

[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: No statistical analyses have been specified for this primary end point.

End point values	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	LEE011(600 mg)+exe(25 mg) esc refractory	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	42	14	
Units: Participants				
Adverse Events (AEs)	41	42	14	
Serious Adverse Events (SAEs)	14	12	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation and Expansion: Overall Response Rate (ORR)

End point title	Dose Escalation and Expansion: Overall Response Rate (ORR)

End point description:

Overall Response Rate (ORR) is defined as the proportion of participants with a best overall response of complete response or partial response.

End point type	Secondary

End point timeframe:

Approximately 6.5 years for Dose Escalation and 4.5 years for Dose Espansion after FPFV

End point values	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	LEE011(600 mg)+exe(25 mg) esc refractory	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	42	14	16
Units: Participants	4	5	2	0

End point values	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	2		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation and Expansion: Disease Control Rate (DCR)

End point title	Dose Escalation and Expansion: Disease Control Rate (DCR)

End point description:

Disease Control Rate (DCR) is the proportion of patients with a best overall response of Complete Response or Partial Response or Stable Disease.

End point type	Secondary

End point timeframe:

Approximately 6.5 years for Dose Escalation and 4.5 years for Dose expansion after FPFV

End point values	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	LEE011(600 mg)+exe(25 mg) esc refractory	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	42	14	16
Units: Participants	27	33	12	13

End point values	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	2		
Units: Participants	7	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation and Expansion: Clinical Benefit Rate (CBR)

End point title	Dose Escalation and Expansion: Clinical Benefit Rate (CBR)

End point description:

Clinical Benefit Rate (CBR) is the Complete Response, Partial Response, or Stable Disease lasting 24 weeks or longer

End point type	Secondary

End point timeframe:

Approximately 6.5 years for Dose Escalation and 4.5 years for Dose Espansion after FPFV

End point values	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	LEE011(600 mg)+exe(25 mg) esc refractory	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	42	14	16
Units: Participants	18	20	10	10

End point values	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	2		
Units: Participants	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Expansion: Duration of Response (DOR)

End point title	Dose Expansion: Duration of Response (DOR)[5]

End point description:

Duration of Response (DOR) is calculated as the time from the date of first documented response (complete response (CR) or partial response (PR)) to the first documented date of progression or death due to underlying cancer. The DOR is not applicable as none of the patients in the expansion treatment groups (triplet treatment naive, triplet treatment refractory and doublet treatment refractory) had a CR or PR

End point type	Secondary

End point timeframe:

Approximately 4.5 years after FPFV

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: No statistical analyses have been specified for this primary end point.

End point values	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	17	2	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Expansion: Progression Free Survival (PFS)

End point title	Dose Expansion: Progression Free Survival (PFS)[6]

End point description:

Progression Free Survival (PFS) is defined as the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

End point type	Secondary

End point timeframe:

Approximately 4.5 years after FPFV

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: No statistical analyses have been specified for this primary end point.

End point values	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) exp refractory	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	17	2	
Units: months				
median (confidence interval 95%)	12.7 (3.7 to 20.2)	1.9 (1.7 to 7.3)	1.7 (-999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 1 of Cycle 1

End point title	Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 1 of Cycle 1

End point description:

AUC0-24h is the area under the drug concentration-time curve during a dosing interval (mass x time x volume-1).

End point type	Secondary

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 1

End point values	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	18	6
Units: hr*ng/mL				

arithmetic mean (standard deviation)	2170 (± 854)	2580 (± 2340)	3750 (± 1840)	2820 (± 1260)

End point values	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	17	6	9
Units: hr*ng/mL				
arithmetic mean (standard deviation)	6810 (± 2280)	5440 (± 2810)	6060 (± 2730)	6380 (± 3630)

End point values	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: hr*ng/mL				
arithmetic mean (standard deviation)	2440 (± 1270)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 15 of Cycle 1

End point title	Dose Escalation: Pharmacokinetics (PK) parameter: AUC0-24h at Day 15 of Cycle 1

End point description:

AUC0-24h is the area under the drug concentration-time curve during a dosing interval (mass x time x volume-1).

End point type	Secondary

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 1

End point values	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	3	13	6
Units: hr*ng/mL				
arithmetic mean (standard deviation)	5310 (± 3760)	4770 (± 3590)	11100 (± 6030)	7120 (± 4240)

End point values	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	16	5	8
Units: hr*ng/mL				
arithmetic mean (standard deviation)	14600 (± 9320)	11500 (± 6550)	10800 (± 3820)	15200 (± 8250)

End point values	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: hr*ng/mL				
arithmetic mean (standard deviation)	6710 (± 2520)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 1 of Cycle 1

End point title	Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 1 of Cycle 1

End point description:

Cmax is the maximum observed drug concentration after drug administration (mass x volume-1).

End point type	Secondary

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 1

End point values	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	18	6
Units: ng/mL				
arithmetic mean (standard deviation)	245 (± 148)	238 (± 180)	397 (± 205)	358 (± 133)

End point values	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	18	6	6
Units: ng/mL				
arithmetic mean (standard deviation)	510 (± 173)	513 (± 206)	512 (± 178)	268 (± 178)

End point values	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ng/mL				
arithmetic mean (standard deviation)	625 (± 310)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 15 of Cycle 1

End point title	Dose Escalation: Pharmacokinetics (PK) parameter: Cmax at Day 15 of Cycle 1

End point description:

Cmax is the maximum observed drug concentration after drug administration (mass x volume-1).

End point type	Secondary

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 15

End point values	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	14	6
Units: ng/mL				
arithmetic mean (standard deviation)	473 (± 305)	315 (± 163)	840 (± 528)	533 (± 277)

End point values	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	16	5	8
Units: ng/mL				
arithmetic mean (standard deviation)	1250 (± 690)	859 (± 459)	893 (± 379)	1030 (± 390)

End point values	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: ng/mL				
arithmetic mean (standard deviation)	550 (± 207)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 1 of Cycle 1

End point title	Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 1 of Cycle 1

End point description:

Tmax is the time to reach maximum plasma/blood/serum drug concentration (time).

End point type	Secondary

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 1

End point values	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	18	6
Units: hour				
median (full range (min-max))	2.56 (1.02 to 4.2)	4.03 (4 to 4.07)	2.81 (0.967 to 4.5)	1.13 (1 to 2.17)

End point values	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	18	6	9
Units: hour				
median (full range (min-max))	4 (1 to 23)	4 (1.95 to 8)	2.82 (1 to 8)	2.1 (1.02 to 4)

End point values	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: hour				
median (full range (min-max))	3.04 (1 to 4.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 15 of Cycle 1

End point title	Dose Escalation: Pharmacokinetics (PK) parameter: Tmax at Day 15 of Cycle 1

End point description:

Tmax is the time to reach maximum plasma/blood/serum drug concentration (time).

End point type	Secondary

End point timeframe:

6 Cycles of treatment (28 day cycles): Cycle 1 Day 15

End point values	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	14	6
Units: hour				
median (full range (min-max))	2.03 (1.03 to 4.12)	2.17 (2.12 to 4.02)	2.19 (0.983 to 4.08)	3.93 (2 to 4.03)

End point values	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	16	5	8
Units: hour				
median (full range (min-max))	3 (1.03 to 4.33)	3.07 (0.983 to 8)	1.98 (1 to 4)	4 (2.05 to 23.4)

End point values	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: hour				
median (full range (min-max))	2 (1 to 4.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation: Pharmacokinetics (PK) parameter: Racc at Day 15 of Cycle 1

End point title	Dose Escalation: Pharmacokinetics (PK) parameter: Racc at Day 15 of Cycle 1
End point description:	
Racc is the accumulation ratio calculated as AUCtau,ss / AUCtau,sd	
End point type	Secondary
End point timeframe:	
6 Cycles of treatment (28 day cycles): Cycle 1 Day 15	

End point values	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (200 mg) + eve (2.5 mg) + exe (25 mg) (fed)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fasting)	LEE011 (250 mg) + eve (2.5 mg) + exe (25 mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	2	13	6
Units: Ratio				
arithmetic mean (standard deviation)	2.22 (± 0.774)	1.55 (± 1.09)	3.54 (± 1.54)	2.54 (± 0.94)

End point values	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fasting)	LEE011 (300 mg) + eve (2.5 mg) + exe (25mg) (fed)	LEE011 (350 mg) + eve (1 mg) + exe (25mg) (fasting)	LEE011 (350 mg) + eve (2.5 mg) + exe (25mg) (fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	16	5	8
Units: Ratio				
arithmetic mean (standard deviation)	2.77 (± 0.846)	2.55 (± 1.02)	2.2 (± 0.618)	2.85 (± 1.17)

End point values	LEE011 (200 mg) + eve (5 mg) + exe (25 mg) (fed)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Ratio				
arithmetic mean (standard deviation)	3.61 (± 0.82)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for approximately 6.5 years for dose escalation and 4.5 years for dose expansion including the 30 days safety follow-up period.

Adverse event reporting additional description:

Any undesirable sign(s), symptom(s), or medical condition(s) that occurred after patient's signed informed consent up to roughly 6.5 years for dose escalation and 4.5 years for dose expansion including the 30 days safety follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive

Reporting group description:

Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered in fasting to the naive to CDK4/6 inhibitors group

Reporting group title	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory

Reporting group description:

Triplet combination of LEE011 200 mg + everolimus (RAD001) 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

Reporting group title	Triplet: ESCALATION ALL

Reporting group description:

Triplet: ESCALATION ALL

Reporting group title	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp naive

Reporting group description:

Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the naive to CDK4/6 inhibitors group

Reporting group title	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory

Reporting group description:

Following RP2D declaration for the triplet combination, LEE011 300 mg + everolimus 2.5 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

Reporting group title	LEE011(600 mg)+exe(25 mg) esc refractory

Reporting group description:

Doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group

Reporting group title	LEE011(600 mg)+exe(25 mg) exp refractory

Reporting group description:

Following RP2D declaration for the doublet combination, LEE011 600 mg + exemestane 25 mg was administered with food to the refractory to CDK4/6 inhibitor based therapy group (except patients with disease refractory to prior LEE011)

Reporting group title	All subjects

Reporting group description:

All subjects

Serious adverse events	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	Triplet: ESCALATION ALL
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 41 (34.15%)	12 / 42 (28.57%)	26 / 83 (31.33%)
number of deaths (all causes)	4	2	6
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Aspiration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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
Dyspnoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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

Blood bilirubin increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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
White blood cell count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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			
Transfusion reaction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Central nervous system inflammation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			

subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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
Stomatitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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

Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	3 / 83 (3.61%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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
Wound infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (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			
Hyperkalaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LEE011(300 mg)+eve(2.5 mg)+exe (25mg)	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) esc refractory
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)	1 / 17 (5.88%)	6 / 14 (42.86%)
number of deaths (all causes)	0	0	3
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant peritoneal neoplasm			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 peritoneum			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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			
Superior vena cava syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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			
Peripheral swelling			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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			
Acute respiratory failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Aspiration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			

subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (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
Haemoptysis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (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
Pleural effusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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	2 / 16 (12.50%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (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
White blood cell count decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Transfusion reaction			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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			
Acute myocardial infarction			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 arrest			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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			
Central nervous system inflammation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Encephalopathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Lymphopenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Thrombocytopenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Enterocolitis			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Small intestinal obstruction			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (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
Stomatitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 gastrointestinal haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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			
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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			
Cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Device related infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Infectious colitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Localised infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (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
Pneumonia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (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
Wound infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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
Hyponatraemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (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	LEE011(600 mg)+exe(25 mg) exp refractory	All subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	38 / 132 (28.79%)	
number of deaths (all causes)	0	9	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Aspiration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

White blood cell count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Transfusion reaction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system inflammation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Small intestinal obstruction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	6 / 132 (4.55%)	
occurrences causally related to treatment / all	0 / 0	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 2 (50.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (fasting) esc naive	LEE011(200 mg)+eve(2.5 mg)+exe (25mg) (FED) esc refractory	Triplet: ESCALATION ALL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	42 / 42 (100.00%)	83 / 83 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	3 / 83 (3.61%)
occurrences (all)	1	2	3
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Tumour pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Hot flush			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	3 / 83 (3.61%)
occurrences (all)	0	4	4
Hypertension			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	6 / 83 (7.23%)
occurrences (all)	3	3	6
Hypotension			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Lymphoedema			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	6 / 83 (7.23%)
occurrences (all)	3	3	6
Phlebitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 41 (17.07%)	7 / 42 (16.67%)	14 / 83 (16.87%)
occurrences (all)	9	12	21
Axillary pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Chest discomfort			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Chest pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Chills			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 83 (3.61%)
occurrences (all)	2	1	3
Fatigue			

subjects affected / exposed	15 / 41 (36.59%)	9 / 42 (21.43%)	24 / 83 (28.92%)
occurrences (all)	16	11	27
Feeling cold			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Gait disturbance			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Local swelling			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Mass			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Mucosal dryness			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Non-cardiac chest pain			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 83 (3.61%)
occurrences (all)	2	1	3
Oedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	10 / 41 (24.39%)	5 / 42 (11.90%)	15 / 83 (18.07%)
occurrences (all)	12	6	18
Pain			
subjects affected / exposed	1 / 41 (2.44%)	3 / 42 (7.14%)	4 / 83 (4.82%)
occurrences (all)	2	3	5
Peripheral swelling			

subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	7 / 41 (17.07%)	7 / 42 (16.67%)	14 / 83 (16.87%)
occurrences (all)	7	11	18
Xerosis			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	2	0	2
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Seasonal allergy			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	2	0	2
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Breast pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Menopausal symptoms			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Pelvic pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Vaginal discharge			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Vulval ulceration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Vulvovaginal burning sensation			

subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	2	2
Vulvovaginal pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Allergic sinusitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	12 / 41 (29.27%)	11 / 42 (26.19%)	23 / 83 (27.71%)
occurrences (all)	14	11	25
Dysphonia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 42 (0.00%)	3 / 83 (3.61%)
occurrences (all)	4	0	4
Dyspnoea			
subjects affected / exposed	10 / 41 (24.39%)	10 / 42 (23.81%)	20 / 83 (24.10%)
occurrences (all)	12	10	22
Dyspnoea exertional			
subjects affected / exposed	4 / 41 (9.76%)	1 / 42 (2.38%)	5 / 83 (6.02%)
occurrences (all)	4	2	6
Epistaxis			
subjects affected / exposed	9 / 41 (21.95%)	7 / 42 (16.67%)	16 / 83 (19.28%)
occurrences (all)	15	10	25
Haemoptysis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Hiccups			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Nasal congestion			

subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	5 / 83 (6.02%)
occurrences (all)	3	3	6
Nasal discharge discolouration			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Nasal dryness			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	2 / 83 (2.41%)
occurrences (all)	0	2	2
Oropharyngeal pain			
subjects affected / exposed	3 / 41 (7.32%)	4 / 42 (9.52%)	7 / 83 (8.43%)
occurrences (all)	3	4	7
Painful respiration			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	2	0	2
Paranasal sinus discomfort			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Pharyngeal inflammation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Pleural effusion			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	3 / 83 (3.61%)
occurrences (all)	1	2	3
Pneumonitis			
subjects affected / exposed	4 / 41 (9.76%)	5 / 42 (11.90%)	9 / 83 (10.84%)
occurrences (all)	4	7	11
Productive cough			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	2	2
Pulmonary congestion			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Reflux laryngitis			

subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	2 / 83 (2.41%)
occurrences (all)	0	2	2
Rhinorrhoea			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Sinus congestion			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Sinus pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Throat irritation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	3	0	3
Delirium			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	2	2	4
Depressive symptom			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1

Insomnia			
subjects affected / exposed	2 / 41 (4.88%)	6 / 42 (14.29%)	8 / 83 (9.64%)
occurrences (all)	2	7	9
Irritability			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Restlessness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Investigations			
Alanine aminotransferase decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	12 / 41 (29.27%)	13 / 42 (30.95%)	25 / 83 (30.12%)
occurrences (all)	19	19	38
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 41 (43.90%)	16 / 42 (38.10%)	34 / 83 (40.96%)
occurrences (all)	30	24	54
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 41 (26.83%)	7 / 42 (16.67%)	18 / 83 (21.69%)
occurrences (all)	18	11	29
Blood bilirubin increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Blood calcium decreased			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	2 / 83 (2.41%)
occurrences (all)	0	6	6
Blood chloride decreased			

subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Blood cholesterol increased			
subjects affected / exposed	4 / 41 (9.76%)	3 / 42 (7.14%)	7 / 83 (8.43%)
occurrences (all)	6	8	14
Blood creatinine increased			
subjects affected / exposed	4 / 41 (9.76%)	5 / 42 (11.90%)	9 / 83 (10.84%)
occurrences (all)	10	10	20
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	5 / 83 (6.02%)
occurrences (all)	3	2	5
Blood phosphorus decreased			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Blood phosphorus increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Blood sodium decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	3	0	3
Blood triglycerides increased			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	3 / 83 (3.61%)
occurrences (all)	2	3	5
Blood urea decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			

subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	2	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 41 (12.20%)	5 / 42 (11.90%)	10 / 83 (12.05%)
occurrences (all)	7	5	12
Haematocrit			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Haemoglobin decreased			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	2	0	2
International normalised ratio increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Lymphocyte count decreased			
subjects affected / exposed	12 / 41 (29.27%)	11 / 42 (26.19%)	23 / 83 (27.71%)
occurrences (all)	19	30	49
Lymphocyte count increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	20 / 41 (48.78%)	16 / 42 (38.10%)	36 / 83 (43.37%)
occurrences (all)	40	48	88
Neutrophil count increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Platelet count decreased			
subjects affected / exposed	9 / 41 (21.95%)	8 / 42 (19.05%)	17 / 83 (20.48%)
occurrences (all)	16	10	26
Platelet count increased			

subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Thyroxine decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Thyroxine free increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Transaminases increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Tri-iodothyronine increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	6 / 41 (14.63%)	3 / 42 (7.14%)	9 / 83 (10.84%)
occurrences (all)	8	3	11
Weight increased			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
White blood cell count decreased			
subjects affected / exposed	20 / 41 (48.78%)	17 / 42 (40.48%)	37 / 83 (44.58%)
occurrences (all)	36	32	68
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Fall			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Ligament sprain			

subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Muscle rupture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Radiation skin injury			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Rib fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Wound			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Wound secretion			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Wrist fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Bradycardia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Diastolic dysfunction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Palpitations			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2

Sinus tachycardia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Tachycardia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	2 / 83 (2.41%)
occurrences (all)	0	2	2
Ventricular extrasystoles			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Aphonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Ataxia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Cognitive disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	4 / 83 (4.82%)
occurrences (all)	3	1	4
Dysaesthesia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	8 / 41 (19.51%)	4 / 42 (9.52%)	12 / 83 (14.46%)
occurrences (all)	8	4	12
Headache			
subjects affected / exposed	6 / 41 (14.63%)	11 / 42 (26.19%)	17 / 83 (20.48%)
occurrences (all)	6	16	22
Hyperaesthesia			

subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Intracranial aneurysm			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Neuropathy peripheral			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	2	0	2
Restless legs syndrome			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Sciatica			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Tremor			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 41 (63.41%)	22 / 42 (52.38%)	48 / 83 (57.83%)
occurrences (all)	43	48	91

Iron deficiency anaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Leukopenia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 42 (7.14%)	4 / 83 (4.82%)
occurrences (all)	1	3	4
Lymphopenia			
subjects affected / exposed	11 / 41 (26.83%)	5 / 42 (11.90%)	16 / 83 (19.28%)
occurrences (all)	14	6	20
Neutropenia			
subjects affected / exposed	18 / 41 (43.90%)	22 / 42 (52.38%)	40 / 83 (48.19%)
occurrences (all)	33	40	73
Thrombocytopenia			
subjects affected / exposed	12 / 41 (29.27%)	12 / 42 (28.57%)	24 / 83 (28.92%)
occurrences (all)	20	31	51
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	2	0	2
Vertigo			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Eye disorders			
Cataract			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Chalazion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Dry eye			

subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 83 (3.61%)
occurrences (all)	2	1	3
Eye pruritus			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Eyelid oedema			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Lacrimation increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Myopia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Visual impairment			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Abdominal distension			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	4 / 41 (9.76%)	5 / 42 (11.90%)	9 / 83 (10.84%)
occurrences (all)	4	9	13
Abdominal pain upper			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	4 / 83 (4.82%)
occurrences (all)	6	1	7
Anal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1

Anal incontinence			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	2 / 83 (2.41%)
occurrences (all)	0	2	2
Ascites			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	3 / 83 (3.61%)
occurrences (all)	0	7	7
Atrophic glossitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Cheilitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Colitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	10 / 41 (24.39%)	4 / 42 (9.52%)	14 / 83 (16.87%)
occurrences (all)	12	7	19
Dental caries			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	9 / 41 (21.95%)	13 / 42 (30.95%)	22 / 83 (26.51%)
occurrences (all)	12	19	31
Dry mouth			
subjects affected / exposed	2 / 41 (4.88%)	5 / 42 (11.90%)	7 / 83 (8.43%)
occurrences (all)	2	5	7
Dyspepsia			
subjects affected / exposed	4 / 41 (9.76%)	4 / 42 (9.52%)	8 / 83 (9.64%)
occurrences (all)	4	4	8
Dysphagia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1

Eructation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Flatulence			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Food poisoning			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 83 (3.61%)
occurrences (all)	2	1	3
Gingival pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Gingival ulceration			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	1 / 41 (2.44%)	3 / 42 (7.14%)	4 / 83 (4.82%)
occurrences (all)	1	4	5
Lip oedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	2	2
Lip swelling			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Lip ulceration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	2	5	7

Nausea			
subjects affected / exposed	15 / 41 (36.59%)	12 / 42 (28.57%)	27 / 83 (32.53%)
occurrences (all)	23	15	38
Odynophagia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 42 (7.14%)	4 / 83 (4.82%)
occurrences (all)	1	4	5
Oral pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Rectal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Steatorrhoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	23 / 41 (56.10%)	25 / 42 (59.52%)	48 / 83 (57.83%)
occurrences (all)	39	43	82
Toothache			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	12 / 41 (29.27%)	7 / 42 (16.67%)	19 / 83 (22.89%)
occurrences (all)	16	17	33
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Hepatic necrosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Hepatocellular injury			

subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	4 / 83 (4.82%)
occurrences (all)	2	2	4
Hepatomegaly			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Alopecia			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	5 / 83 (6.02%)
occurrences (all)	2	3	5
Angioedema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	4	4
Dermal cyst			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Dermatitis acneiform			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	3 / 83 (3.61%)
occurrences (all)	1	2	3
Dry skin			
subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	5 / 83 (6.02%)
occurrences (all)	3	3	6
Ecchymosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1

Erythema			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	4 / 83 (4.82%)
occurrences (all)	2	2	4
Hair texture abnormal			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Madarosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Nail discolouration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	4 / 83 (4.82%)
occurrences (all)	3	1	4
Nail dystrophy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Nail toxicity			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Night sweats			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 83 (3.61%)
occurrences (all)	2	1	3
Onychoclasis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	2 / 83 (2.41%)
occurrences (all)	0	2	2
Onychomalacia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Palmoplantar keratoderma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Pigmentation disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	6 / 83 (7.23%)
occurrences (all)	3	3	6
Rash			
subjects affected / exposed	8 / 41 (19.51%)	10 / 42 (23.81%)	18 / 83 (21.69%)
occurrences (all)	11	11	22
Rash erythematous			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Rash macular			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Rash maculo-papular			
subjects affected / exposed	3 / 41 (7.32%)	4 / 42 (9.52%)	7 / 83 (8.43%)
occurrences (all)	4	5	9
Rash vesicular			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Rosacea			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Skin hypopigmentation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Skin lesion			

subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Skin mass			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Skin toxicity			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Yellow skin			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 83 (3.61%)
occurrences (all)	2	1	3
Leukocyturia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Micturition urgency			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Pollakiuria			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Proteinuria			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Renal failure			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Renal impairment			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Urinary incontinence			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 41 (12.20%)	9 / 42 (21.43%)	14 / 83 (16.87%)
occurrences (all)	7	10	17
Arthropathy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	6 / 41 (14.63%)	3 / 42 (7.14%)	9 / 83 (10.84%)
occurrences (all)	6	6	12
Bone cyst			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	5 / 41 (12.20%)	2 / 42 (4.76%)	7 / 83 (8.43%)
occurrences (all)	5	2	7
Bursitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Intervertebral disc degeneration			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Muscle contracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Muscle fatigue			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Muscle spasms			
subjects affected / exposed	2 / 41 (4.88%)	1 / 42 (2.38%)	3 / 83 (3.61%)
occurrences (all)	2	1	3
Musculoskeletal chest pain			

subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	4 / 83 (4.82%)
occurrences (all)	2	3	5
Musculoskeletal pain			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	4 / 83 (4.82%)
occurrences (all)	3	1	4
Musculoskeletal stiffness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	5 / 83 (6.02%)
occurrences (all)	2	3	5
Neck pain			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	2	0	2
Osteitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Osteoarthritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Osteonecrosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Osteopenia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	5 / 83 (6.02%)
occurrences (all)	7	2	9
Pain in jaw			

subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	2 / 83 (2.41%)
occurrences (all)	0	2	2
Trigger finger			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	2	0	2
Atypical pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Bronchitis			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	2	0	2
Cellulitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Clostridium difficile colitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	2	2
Cystitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Device related infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Diverticulitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1

Escherichia urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	2	2
Folliculitis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Fungal infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Gastroenteritis viral			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Genital herpes			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Gingivitis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	5	1	6
Herpes zoster			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Influenza			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Lung infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0

Mastitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Nail infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Neutropenic infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Onychomycosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Paronychia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	3 / 83 (3.61%)
occurrences (all)	2	2	4
Pneumonia			
subjects affected / exposed	4 / 41 (9.76%)	2 / 42 (4.76%)	6 / 83 (7.23%)
occurrences (all)	4	2	6
Rash pustular			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	3	0	3
Respiratory tract infection viral			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1

Sepsis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Sinusitis			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	4 / 83 (4.82%)
occurrences (all)	2	2	4
Skin infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	1 / 83 (1.20%)
occurrences (all)	0	1	1
Tooth infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	4 / 42 (9.52%)	5 / 83 (6.02%)
occurrences (all)	3	10	13
Urinary tract infection			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	5 / 83 (6.02%)
occurrences (all)	2	3	5
Viral infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	4 / 42 (9.52%)	5 / 83 (6.02%)
occurrences (all)	1	6	7
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Wound infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	10 / 41 (24.39%)	6 / 42 (14.29%)	16 / 83 (19.28%)
occurrences (all)	12	7	19
Dehydration			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Hypercholesterolaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	1 / 83 (1.20%)
occurrences (all)	1	0	1
Hyperglycaemia			
subjects affected / exposed	10 / 41 (24.39%)	14 / 42 (33.33%)	24 / 83 (28.92%)
occurrences (all)	15	23	38
Hyperkalaemia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	4 / 83 (4.82%)
occurrences (all)	2	2	4
Hypermagnesaemia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	2	0	2
Hyperphosphataemia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 42 (2.38%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Hypertriglyceridaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	4 / 83 (4.82%)
occurrences (all)	2	2	4
Hypocalcaemia			
subjects affected / exposed	4 / 41 (9.76%)	5 / 42 (11.90%)	9 / 83 (10.84%)
occurrences (all)	5	8	13
Hypoglycaemia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	2 / 83 (2.41%)
occurrences (all)	3	0	3
Hypokalaemia			
subjects affected / exposed	5 / 41 (12.20%)	6 / 42 (14.29%)	11 / 83 (13.25%)
occurrences (all)	6	7	13
Hypomagnesaemia			

subjects affected / exposed	5 / 41 (12.20%)	4 / 42 (9.52%)	9 / 83 (10.84%)
occurrences (all)	9	7	16
Hyponatraemia			
subjects affected / exposed	5 / 41 (12.20%)	7 / 42 (16.67%)	12 / 83 (14.46%)
occurrences (all)	7	7	14
Hypophosphataemia			
subjects affected / exposed	10 / 41 (24.39%)	12 / 42 (28.57%)	22 / 83 (26.51%)
occurrences (all)	22	17	39
Increased appetite			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	3 / 83 (3.61%)
occurrences (all)	0	3	3

Non-serious adverse events	LEE011(300 mg)+eve(2.5 mg)+exe (25mg)	LEE011(300 mg)+eve(2.5 mg)+exe (25mg) exp refractory	LEE011(600 mg)+exe(25 mg) esc refractory
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	17 / 17 (100.00%)	14 / 14 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	1 / 16 (6.25%)	2 / 17 (11.76%)	3 / 14 (21.43%)
occurrences (all)	1	2	4

Hypertension			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	1	1	2
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Phlebitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 16 (18.75%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	10	1	7
Axillary pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 16 (0.00%)	2 / 17 (11.76%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	5 / 16 (31.25%)	9 / 17 (52.94%)	5 / 14 (35.71%)
occurrences (all)	5	11	5
Feeling cold			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			

subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Local swelling			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Mass			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Mucosal dryness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Non-cardiac chest pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	5 / 16 (31.25%)	5 / 17 (29.41%)	2 / 14 (14.29%)
occurrences (all)	5	5	2
Pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	3 / 16 (18.75%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	5	0	1
Xerosis			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Breast pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Menopausal symptoms			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vaginal discharge			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vulval ulceration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal burning sensation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal pain			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Allergic sinusitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	3 / 16 (18.75%)	3 / 17 (17.65%)	4 / 14 (28.57%)
occurrences (all)	3	3	4
Dysphonia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	4 / 16 (25.00%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	4	1	2
Dyspnoea exertional			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	4 / 14 (28.57%)
occurrences (all)	2	1	4
Epistaxis			
subjects affected / exposed	4 / 16 (25.00%)	3 / 17 (17.65%)	1 / 14 (7.14%)
occurrences (all)	4	4	1
Haemoptysis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Nasal discharge discolouration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 17 (11.76%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Painful respiration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Paranasal sinus discomfort			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pharyngeal inflammation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	6 / 16 (37.50%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	6	1	1
Productive cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Pulmonary congestion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Reflux laryngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			

subjects affected / exposed	3 / 16 (18.75%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	5	0	0
Sinus congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Sinus pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
Delirium			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Depressive symptom			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 17 (11.76%)	2 / 14 (14.29%)
occurrences (all)	0	3	6
Irritability			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Nightmare			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	5 / 16 (31.25%)	4 / 17 (23.53%)	5 / 14 (35.71%)
occurrences (all)	6	6	5
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 16 (25.00%)	5 / 17 (29.41%)	8 / 14 (57.14%)
occurrences (all)	5	14	10
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	4 / 14 (28.57%)
occurrences (all)	1	4	4
Blood bilirubin increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
Blood calcium decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood chloride decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	6	0	0
Blood creatinine increased			

subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	5	4	7
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood sodium decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood urea decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	0	1	3
Gamma-glutamyltransferase increased			

subjects affected / exposed	3 / 16 (18.75%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	4	0	0
Haematocrit			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	6 / 16 (37.50%)	1 / 17 (5.88%)	4 / 14 (28.57%)
occurrences (all)	15	1	5
Lymphocyte count increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	10 / 16 (62.50%)	8 / 17 (47.06%)	9 / 14 (64.29%)
occurrences (all)	29	30	23
Neutrophil count increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	1 / 16 (6.25%)	3 / 17 (17.65%)	3 / 14 (21.43%)
occurrences (all)	1	6	3
Platelet count increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Thyroxine decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Thyroxine free increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Transaminases increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Tri-iodothyronine increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Weight increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
White blood cell count decreased			
subjects affected / exposed	5 / 16 (31.25%)	6 / 17 (35.29%)	12 / 14 (85.71%)
occurrences (all)	10	16	15
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Muscle rupture			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Post procedural haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Radiation skin injury			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rib fracture			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Wound secretion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Wrist fracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Diastolic dysfunction			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Ventricular extrasystoles			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0

Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Aphonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Ataxia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 16 (0.00%)	2 / 17 (11.76%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Dysaesthesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	4 / 16 (25.00%)	2 / 17 (11.76%)	0 / 14 (0.00%)
occurrences (all)	4	2	0
Headache			
subjects affected / exposed	3 / 16 (18.75%)	3 / 17 (17.65%)	3 / 14 (21.43%)
occurrences (all)	10	3	3
Hyperaesthesia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Intracranial aneurysm			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Migraine			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 16 (62.50%)	5 / 17 (29.41%)	9 / 14 (64.29%)
occurrences (all)	18	6	13
Iron deficiency anaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	1 / 16 (6.25%)	2 / 17 (11.76%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
Lymphopenia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	4 / 14 (28.57%)
occurrences (all)	6	1	6

Neutropenia			
subjects affected / exposed	10 / 16 (62.50%)	11 / 17 (64.71%)	6 / 14 (42.86%)
occurrences (all)	27	15	17
Thrombocytopenia			
subjects affected / exposed	6 / 16 (37.50%)	4 / 17 (23.53%)	4 / 14 (28.57%)
occurrences (all)	12	14	7
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Ear discomfort			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Ear pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Chalazion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Eye pruritus			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Lacrimation increased			

subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Myopia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 16 (0.00%)	2 / 17 (11.76%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Visual impairment			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Abdominal pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 17 (11.76%)	0 / 14 (0.00%)
occurrences (all)	0	4	0
Abdominal pain upper			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Anal haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Anal incontinence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Aphthous ulcer			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Ascites			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Atrophic glossitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	3 / 16 (18.75%)	3 / 17 (17.65%)	6 / 14 (42.86%)
occurrences (all)	3	3	8
Dental caries			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	2 / 16 (12.50%)	5 / 17 (29.41%)	8 / 14 (57.14%)
occurrences (all)	3	7	13
Dry mouth			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Dyspepsia			
subjects affected / exposed	2 / 16 (12.50%)	2 / 17 (11.76%)	1 / 14 (7.14%)
occurrences (all)	2	3	1
Dysphagia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Food poisoning			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 16 (25.00%)	0 / 17 (0.00%)	3 / 14 (21.43%)
occurrences (all)	4	0	3
Gingival pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Gingival ulceration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Lip oedema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lip swelling			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lip ulceration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	5 / 16 (31.25%)	9 / 17 (52.94%)	6 / 14 (42.86%)
occurrences (all)	9	10	7
Odynophagia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Rectal haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Steatorrhoea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	9 / 16 (56.25%)	11 / 17 (64.71%)	4 / 14 (28.57%)
occurrences (all)	25	14	5
Toothache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	3 / 16 (18.75%)	6 / 17 (35.29%)	4 / 14 (28.57%)
occurrences (all)	4	9	4
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hepatic necrosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hepatocellular injury			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hepatomegaly			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 17 (11.76%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	3 / 14 (21.43%)
occurrences (all)	1	1	3
Angioedema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Dermatitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dermatitis acneiform			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	2	1	3
Ecchymosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Madarosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

Nail discolouration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nail disorder			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	2
Nail dystrophy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nail toxicity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Onychoclasis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Onychomalacia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Palmoplantar keratoderma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pigmentation disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pruritus			

subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	5 / 16 (31.25%)	4 / 17 (23.53%)	1 / 14 (7.14%)
occurrences (all)	6	5	1
Rash erythematous			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Rash maculo-papular			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rash vesicular			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Rosacea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin hypopigmentation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Skin mass			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin toxicity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Yellow skin			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Leukocyturia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Proteinuria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Renal impairment			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 16 (6.25%)	5 / 17 (29.41%)	2 / 14 (14.29%)
occurrences (all)	2	5	3
Arthropathy			

subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	3 / 14 (21.43%)
occurrences (all)	2	1	5
Bone cyst			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Bursitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc degeneration			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Muscle contracture			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Muscle fatigue			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	1	1	5
Musculoskeletal chest pain			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	2	1	1
Musculoskeletal pain			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	2	3	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Myalgia			

subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	2 / 14 (14.29%)
occurrences (all)	0	3	2
Neck pain			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Osteitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Osteonecrosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Osteoporosis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	2	1	1
Pain in jaw			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Trigger finger			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Atypical pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Gastroenteritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Genital herpes			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lung infection			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Mastitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nail infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1

Neutropenic infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Sepsis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	0	4	1
Skin infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Tooth abscess			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	3 / 17 (17.65%)	1 / 14 (7.14%)
occurrences (all)	2	6	1
Viral infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Wound infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 16 (31.25%)	6 / 17 (35.29%)	1 / 14 (7.14%)
occurrences (all)	5	6	1
Dehydration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			

subjects affected / exposed	3 / 16 (18.75%)	4 / 17 (23.53%)	5 / 14 (35.71%)
occurrences (all)	3	4	6
Hyperkalaemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Hypermagnesaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	3 / 14 (21.43%)
occurrences (all)	1	1	3
Hypomagnesaemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 17 (5.88%)	1 / 14 (7.14%)
occurrences (all)	1	1	2
Hyponatraemia			
subjects affected / exposed	3 / 16 (18.75%)	0 / 17 (0.00%)	2 / 14 (14.29%)
occurrences (all)	3	0	3
Hypophosphataemia			
subjects affected / exposed	5 / 16 (31.25%)	4 / 17 (23.53%)	3 / 14 (21.43%)
occurrences (all)	8	8	5
Increased appetite			

subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 16 (0.00%)	0 / 17 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	LEE011(600 mg)+exe(25 mg) exp refractory	All subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	132 / 132 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Malignant peritoneal neoplasm			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tumour pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Hot flush			
subjects affected / exposed	1 / 2 (50.00%)	10 / 132 (7.58%)	
occurrences (all)	1	12	
Hypertension			
subjects affected / exposed	0 / 2 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	10	
Hypotension			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lymphoedema			
subjects affected / exposed	0 / 2 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	8	

Phlebitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)	20 / 132 (15.15%)	
occurrences (all)	0	39	
Axillary pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Chest pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 2 (50.00%)	6 / 132 (4.55%)	
occurrences (all)	1	6	
Fatigue			
subjects affected / exposed	0 / 2 (0.00%)	43 / 132 (32.58%)	
occurrences (all)	0	48	
Feeling cold			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Local swelling			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Malaise			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Mass			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Mucosal dryness			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Non-cardiac chest pain			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Oedema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 2 (0.00%)	27 / 132 (20.45%)	
occurrences (all)	0	30	
Pain			
subjects affected / exposed	0 / 2 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	6	
Peripheral swelling			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	2 / 2 (100.00%)	20 / 132 (15.15%)	
occurrences (all)	2	26	
Xerosis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Seasonal allergy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	

Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Breast pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Menopausal symptoms			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vaginal discharge			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vulval ulceration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vulvovaginal dryness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Vulvovaginal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Allergic sinusitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 2 (50.00%)	34 / 132 (25.76%)	
occurrences (all)	1	36	
Dysphonia			

subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	5	
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	27 / 132 (20.45%)	
occurrences (all)	0	29	
Dyspnoea exertional			
subjects affected / exposed	0 / 2 (0.00%)	12 / 132 (9.09%)	
occurrences (all)	0	13	
Epistaxis			
subjects affected / exposed	0 / 2 (0.00%)	24 / 132 (18.18%)	
occurrences (all)	0	34	
Haemoptysis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hiccups			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 2 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	8	
Nasal discharge discolouration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nasal dryness			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 2 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	10	
Painful respiration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Paranasal sinus discomfort			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Pharyngeal inflammation			

subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Pleural effusion			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Pneumonitis			
subjects affected / exposed	0 / 2 (0.00%)	17 / 132 (12.88%)	
occurrences (all)	0	19	
Productive cough			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	4	
Pulmonary congestion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Reflux laryngitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Rhinorrhoea			
subjects affected / exposed	0 / 2 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	7	
Sinus congestion			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Sinus pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	7	
Delirium			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 2 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	7	
Depressive symptom			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 2 (0.00%)	12 / 132 (9.09%)	
occurrences (all)	0	18	
Irritability			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nightmare			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Investigations			
Alanine aminotransferase decreased			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	39 / 132 (29.55%)	
occurrences (all)	0	55	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	51 / 132 (38.64%)	
occurrences (all)	0	83	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 2 (0.00%)	24 / 132 (18.18%)	
occurrences (all)	0	38	
Blood bilirubin increased			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Blood calcium decreased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	6	
Blood chloride decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Blood cholesterol increased			
subjects affected / exposed	0 / 2 (0.00%)	9 / 132 (6.82%)	
occurrences (all)	0	20	
Blood creatinine increased			
subjects affected / exposed	1 / 2 (50.00%)	15 / 132 (11.36%)	
occurrences (all)	1	37	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 2 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	5	
Blood phosphorus decreased			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Blood phosphorus increased			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Blood sodium decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	4	
Blood triglycerides increased			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	5	
Blood urea decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Ejection fraction decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 2 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	6	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	13 / 132 (9.85%)	
occurrences (all)	0	16	
Haematocrit			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
International normalised ratio increased			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 2 (0.00%)	34 / 132 (25.76%)	
occurrences (all)	0	70	
Lymphocyte count increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	1 / 2 (50.00%)	64 / 132 (48.48%)	
occurrences (all)	1	171	
Neutrophil count increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	0 / 2 (0.00%)	24 / 132 (18.18%)	
occurrences (all)	0	36	
Platelet count increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Thyroxine decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Thyroxine free increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Tri-iodothyronine increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 2 (0.00%)	11 / 132 (8.33%)	
occurrences (all)	0	13	
Weight increased			

subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	5	
White blood cell count decreased			
subjects affected / exposed	0 / 2 (0.00%)	60 / 132 (45.45%)	
occurrences (all)	0	109	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Muscle rupture			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Post procedural haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Radiation skin injury			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Rib fracture			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Wound			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Wound secretion			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Wrist fracture			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Diastolic dysfunction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Sinus tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Ventricular extrasystoles			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Aphonia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Ataxia			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Cognitive disorder			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	6 / 132 (4.55%)	
occurrences (all)	0	6	
Dysaesthesia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Dysgeusia			
subjects affected / exposed	0 / 2 (0.00%)	18 / 132 (13.64%)	
occurrences (all)	0	18	
Headache			
subjects affected / exposed	1 / 2 (50.00%)	27 / 132 (20.45%)	
occurrences (all)	1	39	
Hyperaesthesia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Intracranial aneurysm			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Neuropathy peripheral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Restless legs syndrome			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	72 / 132 (54.55%)	
occurrences (all)	0	128	
Iron deficiency anaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	0 / 2 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	8	
Lymphopenia			
subjects affected / exposed	0 / 2 (0.00%)	23 / 132 (17.42%)	
occurrences (all)	0	33	
Neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	67 / 132 (50.76%)	
occurrences (all)	0	132	
Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	38 / 132 (28.79%)	
occurrences (all)	0	84	
Ear and labyrinth disorders			
Cerumen impaction			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Ear discomfort			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Vertigo			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Chalazion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Eye pruritus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Eyelid oedema			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Lacrimation increased			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Myopia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	4	

Visual impairment			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Abdominal distension			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	11 / 132 (8.33%)	
occurrences (all)	0	17	
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	10	
Anal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Anal incontinence			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	5	
Ascites			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	7	
Atrophic glossitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Cheilitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Colitis			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 2 (50.00%)	27 / 132 (20.45%)	
occurrences (all)	1	34	
Dental caries			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	37 / 132 (28.03%)	
occurrences (all)	0	54	
Dry mouth			
subjects affected / exposed	0 / 2 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	10	
Dyspepsia			
subjects affected / exposed	1 / 2 (50.00%)	14 / 132 (10.61%)	
occurrences (all)	1	15	
Dysphagia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Food poisoning			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 2 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	10	
Gingival pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Gingival ulceration			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	0 / 2 (0.00%)	5 / 132 (3.79%)	
occurrences (all)	0	7	
Lip oedema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Lip swelling			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lip ulceration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	9	
Nausea			
subjects affected / exposed	1 / 2 (50.00%)	48 / 132 (36.36%)	
occurrences (all)	1	65	
Odynophagia			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	5	
Oral pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Rectal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Steatorrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Stomatitis			

subjects affected / exposed	0 / 2 (0.00%)	72 / 132 (54.55%)	
occurrences (all)	0	126	
Toothache			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	33 / 132 (25.00%)	
occurrences (all)	1	51	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hepatic necrosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hepatocellular injury			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Hepatomegaly			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Alopecia			
subjects affected / exposed	0 / 2 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	10	
Angioedema			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	4	
Dermal cyst			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Dermatitis			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Dermatitis acneiform			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Dry skin			
subjects affected / exposed	0 / 2 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	12	
Ecchymosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Hair texture abnormal			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Madarosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nail discolouration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nail disorder			
subjects affected / exposed	0 / 2 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	8	
Nail dystrophy			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nail toxicity			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Onychoclasis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Onychomalacia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pain of skin			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Palmoplantar keratoderma			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pigmentation disorder			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	8	
Rash			
subjects affected / exposed	0 / 2 (0.00%)	28 / 132 (21.21%)	
occurrences (all)	0	34	
Rash erythematous			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	

Rash macular			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	3	
Rash maculo-papular			
subjects affected / exposed	0 / 2 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	9	
Rash vesicular			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Rosacea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Skin hyperpigmentation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Skin hypopigmentation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Skin mass			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Skin toxicity			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Yellow skin			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 2 (50.00%)	4 / 132 (3.03%)	
occurrences (all)	1	4	
Leukocyturia			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Micturition urgency			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	3	
Proteinuria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Renal impairment			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Urinary incontinence			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)	22 / 132 (16.67%)	
occurrences (all)	0	27	
Arthropathy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 2 (50.00%)	16 / 132 (12.12%)	
occurrences (all)	1	21	
Bone cyst			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	0 / 2 (0.00%)	9 / 132 (6.82%)	
occurrences (all)	0	9	
Bursitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Muscle contracture			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Muscle fatigue			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 2 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	10	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 2 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	9	
Musculoskeletal pain			
subjects affected / exposed	0 / 2 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	10	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 2 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	10	
Neck pain			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Osteitis			

subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Osteoarthritis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Osteonecrosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Osteopenia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Osteoporosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 2 (0.00%)	9 / 132 (6.82%)	
occurrences (all)	0	13	
Pain in jaw			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Trigger finger			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Atypical pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	5	

Cellulitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Clostridium difficile colitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Cystitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Device related infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Diverticulitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Folliculitis			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Fungal infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Gastroenteritis viral			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	

Gastrointestinal infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Genital herpes			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Gingivitis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	6	
Herpes zoster			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Mastitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nail infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	4	
Neutropenic infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Onychomycosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	

Oral candidiasis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	4	
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	6 / 132 (4.55%)	
occurrences (all)	0	6	
Rash pustular			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	3	
Respiratory tract infection viral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	3	
Sepsis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 2 (0.00%)	6 / 132 (4.55%)	
occurrences (all)	0	9	
Skin infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	

Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	15	
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	14	
Viral infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	7 / 132 (5.30%)	
occurrences (all)	0	9	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Wound infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 2 (0.00%)	28 / 132 (21.21%)	
occurrences (all)	0	31	
Dehydration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	36 / 132 (27.27%)	
occurrences (all)	0	51	
Hyperkalaemia			
subjects affected / exposed	0 / 2 (0.00%)	6 / 132 (4.55%)	
occurrences (all)	0	6	
Hypermagnesaemia			

subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Hyperphosphataemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	3	
Hypoalbuminaemia			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	4	
Hypocalcaemia			
subjects affected / exposed	0 / 2 (0.00%)	10 / 132 (7.58%)	
occurrences (all)	0	14	
Hypoglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	4 / 132 (3.03%)	
occurrences (all)	0	5	
Hypokalaemia			
subjects affected / exposed	0 / 2 (0.00%)	16 / 132 (12.12%)	
occurrences (all)	0	18	
Hypomagnesaemia			
subjects affected / exposed	0 / 2 (0.00%)	12 / 132 (9.09%)	
occurrences (all)	0	20	
Hyponatraemia			
subjects affected / exposed	0 / 2 (0.00%)	17 / 132 (12.88%)	
occurrences (all)	0	20	
Hypophosphataemia			
subjects affected / exposed	0 / 2 (0.00%)	34 / 132 (25.76%)	
occurrences (all)	0	60	
Increased appetite			
subjects affected / exposed	0 / 2 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	0 / 2 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2013	Addition of a cohort of patients during dose escalation to allow a preliminary exploration of the PK and safety of ribociclib when given with food in combination with everolimus and exemestane. Optional biopsies for both pharmacodynamics and for the study of mechanisms of tumor resistance. Extensive examination of the genetic alterations of the tumors treated in the pivotal study of everolimus and exemestane indicated that CDK4/6 activity could be responsible for resistance to hormonal plus mTOR treatment in a number of patients. In order to test this hypothesis as well as to correlate efficacy and resistance with inhibition of the CDK4/6 and mTOR pathways, optional paired biopsies and a biopsy at the time of disease progression were to be performed, if accessible and medically feasible. The ontreatment biopsies measure suppression of the mTOR and CDK 4/6 pathways. Addition of guidelines regarding management of hepatitis B and C infections. Reactivation of hepatitis B (HBV) had been observed in patients with cancer receiving chemotherapy. Sporadic cases of hepatitis B reactivation were also seen in this setting with everolimus. Use of antiviral treatments during anti-cancer therapy had shown to reduce the risk of hepatitis B virus reactivation and associated morbidity and mortality.
26 October 2015	The study design was changed to replace the randomized Phase II part with an expansion part in approximately 45 patients. Additional changes to the protocol include recommendations for dose modification, safety monitoring, concomitant medications, PK sampling, biomarker assessments, inclusion/exclusion criteria. Everolimus exposure increased 2- to 4-fold in the presence of ribociclib. In the expansion triplet combination groups, dose modification guidelines were updated. D Since prolongation of the QT interval is one of the potential toxicities for ribociclib, the eligibility criteria related to cardiac function were modified. Updates were made to the dose adjustment guidelines for QTcF prolongation, hepatobiliary toxicities, hyperglycemia, nausea, emesis and diarrhea, in order to enhance and clarify safety monitoring of patients. D however, for the expansion part of the study both ER-positive and/or PR-positive (HR-positive) breast cancer patients were included in order to be aligned with the overall development strategy for ribociclib. D No clinically significant thyroid adverse events have been reported in ribociclib clinical trials so far. The risk to thyroid gland was removed from the reference safety information for the compound. D Potential risk of hepatic toxicity was observed in patients treated with ribociclib. Updates to monitoring and dose adjustment guidelines for hepatobiliary toxicities including ALT, AST, and TBIL were added. D Additional blood collections for exploratory liver biomarkers to further characterize potential drug-induced liver injury and for circulating tumor DNA to explore molecular alterations were added. D The lists of prohibited concomitant medications were updated. D Survival follow-up was not needed since the Phase II part of the study was being removed with this amendment.

04 January 2017	The RP2D for the triplet combination was determined to be ribociclib 300 mg (once daily, 3 weeks on/1 week off in a 4 week cycle) + everolimus 2.5 mg (once daily) + exemestane 25 mg (once daily) taken with food. Enrollment to the first two expansion groups of the triplet combination (Group 1: CDK4/6i naive patients; Group 2: CDK4/6i refractory patients) had been completed with 16 patients treated in Group 1 and 17 in Group 2 on RP2D. The RP2D for the doublet combination had been confirmed to be ribociclib 600 mg (once daily, 3 weeks on/1 week off in a 4 week cycle) + exemestane 25 mg (once daily) taken without food. Enrollment to the expansion group of the doublet combination (Group 3: CDK4/6i refractory patients excluding patients treated with prior ribociclib) had been completed with 2 patients treated in Group 3 on RP2D. The purpose of this amendment was to close further enrollment to the expansion Group 3 (doublet combination) due to the Sponsor’s decision based on another ongoing study CLEE011XUS18T addressing the same question of the role of CDK4/6 inhibition after failure of prior CDK4/6 inhibitor treatment. This decision was not due to safety reasons. On 14-Oct-2016, an Investigator letter was released to inform Investigators about the closure of enrollment to Group 3. Patients who had been allocated by 21-Oct-2016 were allowed to be screened and enrolled. All patients enrolled in the study were to continue on treatment and post-treatment follow-up until they experienced disease progression or withdrew for other reasons outlined in the protocol. This amendment outlined the reduction in scope of the expansion part of the study and the decrease in the number of patients to be enrolled in Group 3. With this amendment, potential interim analyses had been added to allow early analysis of the data as needed for health authority submission purposes.

06 August 2018	The dose adjustment and management recommendations for QTcF prolongation weer updated. Analyses of preclinical and clinical data with ribociclib demonstrated that ribociclib prolongs the QT interval in a concentration-dependent manner. Moreover, based on the ribociclib exposure-ΔQTcF relationship and the clinical experience in studies CLEE011A2301, CLEE011F2301 and CLEE011E2301, ribociclib dose reduction is an effective strategy for managing ribociclib therapy in patients experiencing QTcF prolongation. Therefore, in order to reduce the risk of subsequent QTcF prolongation in patients experiencing a QTcF between 481-500 msec, ribociclib dosing was to be reduced by 1 dose level with the first occurrence of QTcF ≥ 481 msec. The prohibited concomitant medications were updated according to the Oncology Clinical Pharmacology guidance, drug-drug interaction and co-medication considerations (v07, release date: Jan 2018). Updated the withdrawal of consent language to align with the new Global Data Protection Requirements. Reduced the frequency of tumor evaluations as ongoing patients had been on-treatment for more than 18 months. For dose escalation part, tumor evaluations were to be performed within ± 7 days of Day 1 of Cycles 3, 5, and 7. Subsequent evaluations were to be performed within ± 7 days of Day 1 of every fourth Cycle untill 36 months, then as clinically indicated or sooner if there is clinical evidence of disease progression. For the dose expansion part, tumor evaluations were to be performed every 8 weeks (within ± 7 days of Day 1 of Cycles 3, 5, 7, 9, 11 and so on) during the first 18 months. Subsequent evaluations were to be performed every 12 weeks (within ±7 days) until 36 months, then as clinically indicated or sooner if there was clinical evidence of disease progression.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: