Clinical trial results:
Randomised phase III multicentric study comparing efficacy of doxorubicin with trabectedin followed by trabectedin in non-progressive patients versus doxorubicine alone as first-line therapy in patients with metastatic or unresectable leiomyosarcoma (uterine or soft tissue)

Summary

EudraCT number	2016-002186-56
Trial protocol	FR
Global end of trial date	26 April 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	2016/2410

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Gustave Roussy
Sponsor organisation address	114 Rue Edouard Vaillant, Villejuif, France, 94805
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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	26 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2022
Global end of trial reached?	Yes
Global end of trial date	26 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine and compare the progression-free survival (PFS) of patients treated in first line with doxorubicin alone or with the association of doxorubicin and trabectedin followed by trabectedin for non-progressive patients

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2016
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	France: 150
Worldwide total number of subjects	150
EEA total number of subjects	150

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)	89

From 65 to 84 years	60
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 150 subjects were enrolled in this study, and 1 of them did not receive any therapy.

Period 1

Period 1 title	overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	experimental

Arm description:

Trabectedin was to be administered at the dose of 1.1 mg/m2 via central venous access over 3 hours on day 1 of each 3-week cycle in two treatment periods.Ccommercially available doxorubicin was to be administered at the dose of 60 mg/m2 via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. An injection of pegfilgrastim 6 mg (pegylated G-CSF) per subcutaneous route was given on day 2. During the initial treatment period, trabectedin was to be administered in combination with doxorubicin for a maximum of six cycles or until premature discontinuation of treatment. During the maintenance treatment period, patients with a response after the six cycles of initial treatment were to be given trabectedin at the same dose and schedule as during the initial treatment for a maximum of 17 cycles (12 months) or until premature discontinuation of treatment.

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

Dosage and administration details:

Trabectedin was to be administered (after 20 mg dexamethasone premedication given 30 min before) at the dose of 1.1 mg/m2 via central venous access over 3 hours on day 1 of each 3-week cycle in two treatment periods. During the initial treatment period, trabectedin was to be administered in combination with doxorubicin for a maximum of six cycles or until premature discontinuation of treatment. During the maintenance treatment period, patients with a response after the six cycles of initial treatment were to be given trabectedin at the same dose and schedule as during the initial treatment (even if dose reduction was performed during the initial period) for a maximum of 17 cycles (12 months) or until premature discontinuation of treatment.

Arm title	active comparator

Arm description:

Commercially available doxorubicin was to be administered at the dose of 75 mg/m2 via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. Lenograstim (G-CSF) was administered per subcutaneous route at the dose of 150 µg/m2 once a day from Day 3 to Day 9

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

Dosage and administration details:

Commercially available doxorubicin was to be administered at the dose of 75 mg/m2 via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment.

Number of subjects in period 1	experimental	active comparator
Started	74	76
Completed	60	54
Not completed	14	22
Adverse event, serious fatal	7	3
Consent withdrawn by subject	2	-
randomized but not treated	-	1
progression	5	17
other	-	1

Baseline characteristics

Reporting groups

Reporting group title	experimental

Reporting group description:

Trabectedin was to be administered at the dose of 1.1 mg/m2 via central venous access over 3 hours on day 1 of each 3-week cycle in two treatment periods.Ccommercially available doxorubicin was to be administered at the dose of 60 mg/m2 via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. An injection of pegfilgrastim 6 mg (pegylated G-CSF) per subcutaneous route was given on day 2. During the initial treatment period, trabectedin was to be administered in combination with doxorubicin for a maximum of six cycles or until premature discontinuation of treatment. During the maintenance treatment period, patients with a response after the six cycles of initial treatment were to be given trabectedin at the same dose and schedule as during the initial treatment for a maximum of 17 cycles (12 months) or until premature discontinuation of treatment.

Reporting group title	active comparator

Reporting group description:

Commercially available doxorubicin was to be administered at the dose of 75 mg/m2 via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. Lenograstim (G-CSF) was administered per subcutaneous route at the dose of 150 µg/m2 once a day from Day 3 to Day 9

Reporting group values	experimental	active comparator	Total
Number of subjects	74	76	150
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	59	64	
inter-quartile range (Q1-Q3)	52 to 68	53 to 69	-
Gender categorical Units: Subjects			
Female	53	59	112
Male	21	17	38

Subject analysis sets

Subject analysis set title	Efficacy set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients

Reporting group values	Efficacy set		
Number of subjects	150		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	61		
inter-quartile range (Q1-Q3)	52 to 68		
Gender categorical Units: Subjects			
Female	112		
Male	38		

End points

End points reporting groups

Reporting group title	experimental

Reporting group description:

Trabectedin was to be administered at the dose of 1.1 mg/m2 via central venous access over 3 hours on day 1 of each 3-week cycle in two treatment periods.Ccommercially available doxorubicin was to be administered at the dose of 60 mg/m2 via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. An injection of pegfilgrastim 6 mg (pegylated G-CSF) per subcutaneous route was given on day 2. During the initial treatment period, trabectedin was to be administered in combination with doxorubicin for a maximum of six cycles or until premature discontinuation of treatment. During the maintenance treatment period, patients with a response after the six cycles of initial treatment were to be given trabectedin at the same dose and schedule as during the initial treatment for a maximum of 17 cycles (12 months) or until premature discontinuation of treatment.

Reporting group title	active comparator

Reporting group description:

Commercially available doxorubicin was to be administered at the dose of 75 mg/m2 via central venous access over 10 to 15 minutes on day 1 of each 3-week cycle, for a maximum of six cycles or until premature discontinuation of treatment. Lenograstim (G-CSF) was administered per subcutaneous route at the dose of 150 µg/m2 once a day from Day 3 to Day 9

Subject analysis set title	Efficacy set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients

Primary: Progression -free survival (PFS)

End point title	Progression -free survival (PFS)

End point description:

End point type	Primary

End point timeframe:

24 months

End point values	experimental	active comparator	Efficacy set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	74	76	150	
Units: percentage	30	5	150	

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	active comparator v experimental v Efficacy set

Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.58

Notes:

[1] - LMS-04 met its primary endpoint, demonstrating a statistically significant improvement in progression-free-survival with the doxorubicin + trabectedin combination compared with standard-of-care in first-line treatment of metastatic leiomyosarcomas.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	ARM A
Reporting group description: -	
Reporting group title	ARM B
Reporting group description: -	

Serious adverse events	ARM A	ARM B	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 75 (26.67%)	37 / 74 (50.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia	Additional description: Acute myeloid leukaemia		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic	Additional description: Shock haemorrhagic		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
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			

Extravasation	Additional description: Extravasation		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia	Additional description: Hyperthermia		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema	Additional description: Oedema		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Intermenstrual bleeding	Additional description: Intermenstrual bleeding		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema	Additional description: Acute pulmonary oedema		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis	Additional description: Pneumonitis		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	2 / 75 (2.67%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression	Additional description: Depression		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase abnormal	Additional description: Aspartate aminotransferase abnormal		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased	Additional description: Weight decreased		

subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture	Additional description: Femoral neck fracture		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia	Additional description: Aplasia		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiogenic shock	Additional description: Cardiogenic shock		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	2 / 75 (2.67%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiotoxicity	Additional description: Cardiotoxicity		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction	Additional description: Left ventricular dysfunction		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system lesion	Additional description: Central nervous system lesion		

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia	Additional description: Dementia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial	Additional description: Haemorrhage intracranial		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 75 (2.67%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	3 / 75 (4.00%)	13 / 74 (17.57%)	
occurrences causally related to treatment / all	3 / 3	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	0 / 75 (0.00%)	10 / 74 (13.51%)	
occurrences causally related to treatment / all	0 / 0	14 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia	Additional description: Pancytopenia		

subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	0 / 75 (0.00%)	6 / 74 (8.11%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma	Additional description: Faecaloma		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis	Additional description: Enteritis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer	Additional description: Oesophageal ulcer		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative	Additional description: Oesophagitis ulcerative		

subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus	Additional description: Subileus		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Groin pain	Additional description: Groin pain		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection	Additional description: Device related infection		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis	Additional description: Intervertebral discitis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumococcal sepsis	Additional description: Pneumococcal sepsis		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal	Additional description: Pneumonia pneumococcal		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	2 / 75 (2.67%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis	Additional description: Pyelonephritis		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock	Additional description: Septic shock		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Sepsis		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cell death	Additional description: Cell death		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ARM A	ARM B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 75 (100.00%)	74 / 74 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papilloma	Additional description: Papilloma		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Vascular disorders			
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed	1 / 75 (1.33%)	3 / 74 (4.05%)	
occurrences (all)	14	35	
Flushing	Additional description: Flushing		
subjects affected / exposed	3 / 75 (4.00%)	2 / 74 (2.70%)	
occurrences (all)	12	13	
Hot flush	Additional description: Hot flush		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Jugular vein thrombosis	Additional description: Jugular vein thrombosis		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Lymphoedema	Additional description: Lymphoedema		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	3	
Pallor	Additional description: Pallor		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Superficial vein thrombosis	Additional description: Superficial vein thrombosis		

subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Vascular pain	Additional description: Vascular pain		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Vena cava thrombosis	Additional description: Vena cava thrombosis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	8	
Venous thrombosis	Additional description: Venous thrombosis		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	1	4	
Surgical and medical procedures			
Manual lymphatic drainage	Additional description: Manual lymphatic drainage		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	2 / 75 (2.67%)	6 / 74 (8.11%)	
occurrences (all)	2	11	
Catheter site oedema	Additional description: Catheter site oedema		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	3 / 75 (4.00%)	4 / 74 (5.41%)	
occurrences (all)	7	5	
Chills	Additional description: Chills		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	4	
Discomfort	Additional description: Discomfort		

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	10	
Face oedema	Additional description: Face oedema		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	52 / 75 (69.33%)	66 / 74 (89.19%)	
occurrences (all)	174	451	
Facial pain	Additional description: Facial pain		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
Inflammation	Additional description: Inflammation		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 75 (1.33%)	3 / 74 (4.05%)	
occurrences (all)	1	3	
Medical device site thrombosis	Additional description: Medical device site thrombosis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	26 / 75 (34.67%)	30 / 74 (40.54%)	
occurrences (all)	53	63	
Mucosal toxicity	Additional description: Mucosal toxicity		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	7 / 75 (9.33%)	8 / 74 (10.81%)	
occurrences (all)	22	20	
Oedema	Additional description: Oedema		

subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	5	
Pain	Additional description: Pain		
subjects affected / exposed	5 / 75 (6.67%)	12 / 74 (16.22%)	
occurrences (all)	11	30	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	7 / 75 (9.33%)	18 / 74 (24.32%)	
occurrences (all)	9	24	
Unevaluable event	Additional description: Unevaluable event		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Xerosis	Additional description: Xerosis		
subjects affected / exposed	2 / 75 (2.67%)	3 / 74 (4.05%)	
occurrences (all)	5	4	
Reproductive system and breast disorders			
Breast pain	Additional description: Breast pain		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Gynaecomastia	Additional description: Gynaecomastia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Intermenstrual bleeding	Additional description: Intermenstrual bleeding		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	5	
Pelvic pain	Additional description: Pelvic pain		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	3	1	
Vaginal haemorrhage	Additional description: Vaginal haemorrhage		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Vulvovaginal burning sensation	Additional description: Vulvovaginal burning sensation		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal dryness	Additional description: Vulvovaginal dryness		

subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	15 / 75 (20.00%)	15 / 74 (20.27%)	
occurrences (all)	28	23	
Dysphonia	Additional description: Dysphonia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	9 / 75 (12.00%)	13 / 74 (17.57%)	
occurrences (all)	15	46	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	1 / 75 (1.33%)	5 / 74 (6.76%)	
occurrences (all)	2	42	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	3	
Haemoptysis	Additional description: Haemoptysis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	13	
Hiccups	Additional description: Hiccups		
subjects affected / exposed	1 / 75 (1.33%)	3 / 74 (4.05%)	
occurrences (all)	1	4	
Lung disorder	Additional description: Lung disorder		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Nasal congestion	Additional description: Nasal congestion		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Pleural disorder	Additional description: Pleural disorder		

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Productive cough	Additional description: Productive cough		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	3	
Rhinitis allergic	Additional description: Rhinitis allergic		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Rhinorrhoea	Additional description: Rhinorrhoea		
subjects affected / exposed	2 / 75 (2.67%)	4 / 74 (5.41%)	
occurrences (all)	3	5	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	2 / 75 (2.67%)	6 / 74 (8.11%)	
occurrences (all)	2	12	
Depressed mood	Additional description: Depressed mood		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Depression	Additional description: Depression		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	5	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 75 (1.33%)	3 / 74 (4.05%)	
occurrences (all)	1	11	
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	24 / 75 (32.00%)	71 / 74 (95.95%)	
occurrences (all)	68	720	
Aspartate aminotransferase abnormal	Additional description: Aspartate aminotransferase abnormal		

subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	28	
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	20 / 75 (26.67%)	61 / 74 (82.43%)	
occurrences (all)	50	420	
Blood bilirubin	Additional description: Blood bilirubin		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	25 / 75 (33.33%)	53 / 74 (71.62%)	
occurrences (all)	56	544	
Blood alkaline phosphatase	Additional description: Blood alkaline phosphatase		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	7 / 75 (9.33%)	37 / 74 (50.00%)	
occurrences (all)	11	125	
Blood creatine phosphokinase	Additional description: Blood creatine phosphokinase		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	11	
Blood creatine phosphokinase increased	Additional description: Blood creatine phosphokinase increased		
subjects affected / exposed	10 / 75 (13.33%)	30 / 74 (40.54%)	
occurrences (all)	14	198	
Blood creatinine	Additional description: Blood creatinine		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	11 / 75 (14.67%)	29 / 74 (39.19%)	
occurrences (all)	24	136	
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Blood sodium increased	Additional description: Blood sodium increased		

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Cardiac stress test	Additional description: Cardiac stress test		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Creatinine renal clearance increased	Additional description: Creatinine renal clearance increased		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Ejection fraction decreased	Additional description: Ejection fraction decreased		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	2 / 75 (2.67%)	16 / 74 (21.62%)	
occurrences (all)	3	77	
Haemoglobin	Additional description: Haemoglobin		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Haemoglobin decreased	Additional description: Haemoglobin decreased		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Lymphocyte count	Additional description: Lymphocyte count		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	5	
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	8	
Transaminases	Additional description: Transaminases		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	

Transaminases increased	Additional description: Transaminases increased		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	4	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	1 / 75 (1.33%)	5 / 74 (6.76%)	
occurrences (all)	5	11	
White blood cell count decreased	Additional description: White blood cell count decreased		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Ankle fracture	Additional description: Ankle fracture		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Bone fissure	Additional description: Bone fissure		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	3	0	
Burn oesophageal	Additional description: Burn oesophageal		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Tendon injury	Additional description: Tendon injury		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Tooth fracture	Additional description: Tooth fracture		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Wound complication	Additional description: Wound complication		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Congenital, familial and genetic disorders			
Aplasia	Additional description: Aplasia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	3	0	

Cardiac dysfunction	Additional description: Cardiac dysfunction		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	1 / 75 (1.33%)	3 / 74 (4.05%)	
occurrences (all)	2	3	
Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	2 / 75 (2.67%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Burning sensation	Additional description: Burning sensation		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	6	
Dementia	Additional description: Dementia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	3	
Dysaesthesia	Additional description: Dysaesthesia		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	11 / 75 (14.67%)	10 / 74 (13.51%)	
occurrences (all)	18	41	
Headache	Additional description: Headache		

subjects affected / exposed	8 / 75 (10.67%)	6 / 74 (8.11%)	
occurrences (all)	11	7	
Hemiparesis	Additional description: Hemiparesis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Hypokinesia	Additional description: Hypokinesia		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Migraine	Additional description: Migraine		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	0 / 75 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	9	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	2 / 75 (2.67%)	6 / 74 (8.11%)	
occurrences (all)	4	22	
Presyncope	Additional description: Presyncope		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Sciatica	Additional description: Sciatica		
subjects affected / exposed	2 / 75 (2.67%)	2 / 74 (2.70%)	
occurrences (all)	7	5	
Taste disorder	Additional description: Taste disorder		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Anaemia	Additional description: Anaemia		
subjects affected / exposed	65 / 75 (86.67%)	74 / 74 (100.00%)	
occurrences (all)	315	1555	
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	7 / 75 (9.33%)	10 / 74 (13.51%)	
occurrences (all)	8	15	
Hyperleukocytosis	Additional description: Hyperleukocytosis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	31 / 75 (41.33%)	66 / 74 (89.19%)	
occurrences (all)	91	908	
Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	4 / 75 (5.33%)	8 / 74 (10.81%)	
occurrences (all)	6	22	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	33 / 75 (44.00%)	64 / 74 (86.49%)	
occurrences (all)	71	739	
Pancytopenia	Additional description: Pancytopenia		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	11 / 75 (14.67%)	60 / 74 (81.08%)	
occurrences (all)	20	759	
Ear and labyrinth disorders			
Deafness bilateral	Additional description: Deafness bilateral		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	4	
Ear pain	Additional description: Ear pain		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	7	
Vertigo	Additional description: Vertigo		

subjects affected / exposed	3 / 75 (4.00%)	5 / 74 (6.76%)	
occurrences (all)	5	11	
Eye disorders			
Age-related macular degeneration	Additional description: Age-related macular degeneration		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	18	
Cataract	Additional description: Cataract		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Dry eye	Additional description: Dry eye		
subjects affected / exposed	3 / 75 (4.00%)	4 / 74 (5.41%)	
occurrences (all)	3	7	
Eye disorder	Additional description: Eye disorder		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Lacrimation increased	Additional description: Lacrimation increased		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Ocular discomfort	Additional description: Ocular discomfort		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Noninfective conjunctivitis	Additional description: Noninfective conjunctivitis		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced	Additional description: Visual acuity reduced		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	8	
Xerophthalmia	Additional description: Xerophthalmia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	2 / 75 (2.67%)	15 / 74 (20.27%)	
occurrences (all)	3	24	
Abdominal discomfort	Additional description: Abdominal discomfort		

subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	1	4	
Abdominal pain lower	Additional description: Abdominal pain lower		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	3	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	8 / 75 (10.67%)	4 / 74 (5.41%)	
occurrences (all)	19	4	
Abdominal tenderness	Additional description: Abdominal tenderness		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Aerophagia	Additional description: Aerophagia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Anal incontinence	Additional description: Anal incontinence		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	6 / 75 (8.00%)	0 / 74 (0.00%)	
occurrences (all)	14	0	
Ascites	Additional description: Ascites		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Constipation	Additional description: Constipation		
subjects affected / exposed	18 / 75 (24.00%)	28 / 74 (37.84%)	
occurrences (all)	35	105	
Colitis	Additional description: Colitis		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	11 / 75 (14.67%)	28 / 74 (37.84%)	
occurrences (all)	27	72	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	3 / 75 (4.00%)	2 / 74 (2.70%)	
occurrences (all)	14	16	
Dysphagia	Additional description: Dysphagia		

subjects affected / exposed	2 / 75 (2.67%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Dyschezia	Additional description: Dyschezia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	5 / 75 (6.67%)	7 / 74 (9.46%)	
occurrences (all)	15	13	
Eructation	Additional description: Eructation		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Flatulence	Additional description: Flatulence		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	7	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	4 / 75 (5.33%)	2 / 74 (2.70%)	
occurrences (all)	7	2	
Gastrointestinal pain	Additional description: Gastrointestinal pain		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal motility disorder	Additional description: Gastrointestinal motility disorder		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Gingival bleeding	Additional description: Gingival bleeding		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Haematochezia	Additional description: Haematochezia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Ileus	Additional description: Ileus		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration	Additional description: Mouth ulceration		

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Nausea	Additional description: Nausea		
subjects affected / exposed	47 / 75 (62.67%)	64 / 74 (86.49%)	
occurrences (all)	133	298	
Oral pain	Additional description: Oral pain		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	4	0	
Rectal haemorrhage	Additional description: Rectal haemorrhage		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	1	5	
Salivary hypersecretion	Additional description: Salivary hypersecretion		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Toothache	Additional description: Toothache		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	10 / 75 (13.33%)	43 / 74 (58.11%)	
occurrences (all)	13	91	
Hepatobiliary disorders			
Cholestasis	Additional description: Cholestasis		
subjects affected / exposed	0 / 75 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	6	
Hepatic cytolysis	Additional description: Hepatic cytolysis		
subjects affected / exposed	1 / 75 (1.33%)	7 / 74 (9.46%)	
occurrences (all)	7	14	
Liver disorder	Additional description: Liver disorder		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		

subjects affected / exposed	37 / 75 (49.33%)	33 / 74 (44.59%)	
occurrences (all)	123	154	
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	3 / 75 (4.00%)	5 / 74 (6.76%)	
occurrences (all)	11	9	
Eczema	Additional description: Eczema		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	3	0	
Nail discolouration	Additional description: Nail discolouration		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	3	0	
Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	2 / 75 (2.67%)	3 / 74 (4.05%)	
occurrences (all)	3	27	
Nail dystrophy	Additional description: Nail dystrophy		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Nail ridging	Additional description: Nail ridging		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Nail toxicity	Additional description: Nail toxicity		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Onychalgia	Additional description: Onychalgia		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	3	0	
Onycholysis	Additional description: Onycholysis		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	3	4	
Onychoclasis	Additional description: Onychoclasis		

subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	3	
Onychomadesis	Additional description: Onychomadesis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Palmar-plantar erythrodysaesthesia syndrome		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	3	2	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	1 / 75 (1.33%)	5 / 74 (6.76%)	
occurrences (all)	1	16	
Rash	Additional description: Rash		
subjects affected / exposed	0 / 75 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Rash erythematous	Additional description: Rash erythematous		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	6	
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Skin hyperpigmentation	Additional description: Skin hyperpigmentation		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Skin irritation	Additional description: Skin irritation		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Cystitis noninfective	Additional description: Cystitis noninfective		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Dysuria	Additional description: Dysuria		

subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Haematuria	Additional description: Haematuria		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed	2 / 75 (2.67%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
Renal colic	Additional description: Renal colic		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Renal failure	Additional description: Renal failure		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	4	
Renal pain	Additional description: Renal pain		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Urinary tract obstruction	Additional description: Urinary tract obstruction		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	3 / 75 (4.00%)	11 / 74 (14.86%)	
occurrences (all)	4	34	
Back pain	Additional description: Back pain		
subjects affected / exposed	4 / 75 (5.33%)	9 / 74 (12.16%)	
occurrences (all)	8	21	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	2	3	
Fistula	Additional description: Fistula		

subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Groin pain	Additional description: Groin pain		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	9	
Muscular weakness	Additional description: Muscular weakness		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	3	
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	6	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	5	0	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	3 / 75 (4.00%)	11 / 74 (14.86%)	
occurrences (all)	6	24	
Neck pain	Additional description: Neck pain		
subjects affected / exposed	1 / 75 (1.33%)	5 / 74 (6.76%)	
occurrences (all)	1	14	
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	2 / 75 (2.67%)	1 / 74 (1.35%)	
occurrences (all)	4	2	
Pain in jaw	Additional description: Pain in jaw		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	4 / 75 (5.33%)	3 / 74 (4.05%)	
occurrences (all)	11	6	
Rhabdomyolysis	Additional description: Rhabdomyolysis		

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Spinal pain	Additional description: Spinal pain		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	2 / 75 (2.67%)	4 / 74 (5.41%)	
occurrences (all)	2	6	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	2 / 75 (2.67%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Cystitis	Additional description: Cystitis		
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Device related infection	Additional description: Device related infection		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Ear infection	Additional description: Ear infection		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Enterocolitis infectious	Additional description: Enterocolitis infectious		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Folliculitis	Additional description: Folliculitis		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	5	
Fungal infection	Additional description: Fungal infection		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	11	
Haematoma infection	Additional description: Haematoma infection		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	

Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	3	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Infection	Additional description: Infection		
subjects affected / exposed	2 / 75 (2.67%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Localised infection	Additional description: Localised infection		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	9	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	2 / 75 (2.67%)	4 / 74 (5.41%)	
occurrences (all)	2	5	
Onychomycosis	Additional description: Onychomycosis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Oral fungal infection	Additional description: Oral fungal infection		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Otitis externa	Additional description: Otitis externa		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Pyelonephritis	Additional description: Pyelonephritis		
subjects affected / exposed	2 / 75 (2.67%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	8	

Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Skin infection	Additional description: Skin infection		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Tooth abscess	Additional description: Tooth abscess		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Tracheitis	Additional description: Tracheitis		
subjects affected / exposed	0 / 75 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	2	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	3 / 75 (4.00%)	6 / 74 (8.11%)	
occurrences (all)	3	9	
Viral infection	Additional description: Viral infection		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Viral pharyngitis	Additional description: Viral pharyngitis		
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Viral rhinitis	Additional description: Viral rhinitis		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Cell death	Additional description: Cell death		
subjects affected / exposed	0 / 75 (0.00%)	6 / 74 (8.11%)	
occurrences (all)	0	7	
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	15 / 75 (20.00%)	22 / 74 (29.73%)	
occurrences (all)	34	60	
Dehydration	Additional description: Dehydration		

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Hypercalcaemia	Additional description: Hypercalcaemia		
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	
occurrences (all)	1	12	
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	6	
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	3	
Hypoalbuminaemia	Additional description: Hypoalbuminaemia		
subjects affected / exposed	0 / 75 (0.00%)	5 / 74 (6.76%)	
occurrences (all)	0	12	
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	3	
Hypoglycaemia	Additional description: Hypoglycaemia		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	0 / 75 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	7	
Malnutrition	Additional description: Malnutrition		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2017	The information notice for the patients was modified following the update of the investigator's brochure.
20 April 2018	The information notice for the patients was modified following the update of the investigator's brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported