Clinical trial results:
An open-label first-in-human phase 1/2a study to evaluate safety, feasibility and efficacy of multiple dosing with individualised VB10.NEO or VB10.NEO and bempegaldesleukin (NKTR-214) immunotherapy in patients with locally advanced or metastatic melanoma, NSCLC, clear renal cell carcinoma, urothelial cancer or squamous cell carcinoma of head and neck, who did not reach complete responses with current standard of care immune checkpoint blockade.

Summary

EudraCT number	2017-002474-39
Trial protocol	DE
Global end of trial date	30 January 2023

Results information

Result version number	v2 (current)
This version publication date	24 May 2024
First version publication date	15 February 2024
Version creation reason	• Correction of full data set Mistake in the AE reporting.

Trial information

Trial identification

Sponsor protocol code	VB N-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03548467
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nykode Therapeutics ASA
Sponsor organisation address	Gaustadalléen 21, Oslo, Norway,
Public contact	Medical Expert, Nykode Therapeutics ASA, +47 22958193, storhaug@nykode.com
Scientific contact	Medical Expert, Nykode Therapeutics ASA, +47 22958193, storhaug@nykode.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	30 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2023
Global end of trial reached?	Yes
Global end of trial date	30 January 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety/tolerability of multiple doses of 3 mg VB10.NEO immunotherapy and of multiple doses of
3 mg VB10.NEO immunotherapy in combination with 0.006 mg/kg bempegaldesleukin.

To determine the feasibility of VB10.NEO (overall process feasibility from biopsy, sequencing, neoepitope selection and vaccine manufacturing).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964, and subsequent amendments and International Council for Harmonisation (ICH) Guideline for Good Clinical Practice E6 (R2) (European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use CHMP)/ICH/135/1995), including archiving of essential documents and the EU Clinical Trial Directive (CTD)2001/20/EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 study centres in Germany.

Pre-assignment

Screening details:

Participants were assigned to VB10.NEO treatment in 1 of 5 different arms depending on tumor type. Arm 1: melanoma; Arm 2: non-small cell lung cancer; Arm 3: clear-cell renal carcinoma; Arm 4: urothelial cancer: Arm 5: squamous cell carcinoma of the head and neck. Arm 5 was further divided into 5A and 5B, where Arm 5B also received NKTR-214.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm #1

Arm description:

Melanoma

Arm type	Experimental
Investigational medicinal product name	VB10.NEO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.NEO, 3 mg/dose with 3 vaccinations Q3W during the induction period, followed by maintenance period with vaccinations Q4W for up to 1 year from first immunisation (total of 14 vaccinations).

Arm title	Arm #2

Arm description:

NSCLC

Arm type	Experimental
Investigational medicinal product name	VB10.NEO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.NEO, 3 mg/dose with 3 vaccinations Q3W during the induction period, followed by maintenance period with vaccinations Q4W for up to 1 year from first immunisation (total of 14 vaccinations).

Arm title	Arm #3

Arm description:

RCC

Arm type	Experimental

Investigational medicinal product name	VB10.NEO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.NEO, 3 mg/dose with 3 vaccinations Q3W during the induction period, followed by maintenance period with vaccinations Q4W for up to 1 year from first immunisation (total of 14 vaccinations).

Arm title	Arm #4

Arm description:

Urothelial

Arm type	Experimental
Investigational medicinal product name	VB10.NEO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.NEO, 3 mg/dose with 3 vaccinations Q3W during the induction period, followed by maintenance period with vaccinations Q4W for up to 1 year from first immunisation (total of 14 vaccinations).

Arm title	Arm #5A

Arm description:

SCCHN

Arm type	Experimental
Investigational medicinal product name	VB10.NEO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.NEO, 3 mg/dose with 3 vaccinations Q3W during the induction period, followed by maintenance period with vaccinations Q4W for up to 1 year from first immunisation (total of 14 vaccinations).

Arm title	Arm #5B

Arm description:

SCCHN VB10.NEO and NKTR-214

Arm type	Experimental
Investigational medicinal product name	VB10.NEO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

VB10.NEO, 3 mg/dose with 3 vaccinations Q3W during the induction period, followed by maintenance period with vaccinations Q4W for up to 1 year from first immunisation (total of 14 vaccinations).

Investigational medicinal product name	NKTR-214
Investigational medicinal product code	
Other name	Bempegaldesleukin
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

NKTR-214 (Bempegaldesleukin) 0.006 mg/kg was administered IV starting from Week 11 (Visit 8A or at any dosing visit up to Week 34 [Visit 14]) and up to Week 50 (up to 11 doses). The first 2 doses were in a Q3W interval and the following doses in Q4W intervals.

Number of subjects in period 1	Arm #1	Arm #2	Arm #3
Started	8	5	10
Completed	3	2	7
Not completed	5	3	3
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	-	-	-
Disease progression	1	1	2
Adverse event, non-fatal	-	1	-
Other	2	-	1
Protocol deviation	1	-	-

Number of subjects in period 1	Arm #4	Arm #5A	Arm #5B
Started	4	8	6
Completed	2	2	3
Not completed	2	6	3
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	-	2	-
Disease progression	1	2	2
Adverse event, non-fatal	-	1	-
Other	-	-	1
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm #1
Reporting group description:	
Melanoma	
Reporting group title	Arm #2
Reporting group description:	
NSCLC	
Reporting group title	Arm #3
Reporting group description:	
RCC	
Reporting group title	Arm #4
Reporting group description:	
Urothelial	
Reporting group title	Arm #5A
Reporting group description:	
SCCHN	
Reporting group title	Arm #5B
Reporting group description:	
SCCHN VB10.NEO and NKTR-214	

Reporting group values	Arm #1	Arm #2	Arm #3
Number of subjects	8	5	10
Age categorical Units: Subjects			
Adults (18-64 years)	5	4	7
From 65-84 years	3	1	3
Gender categorical Units: Subjects			
Female	5	3	3
Male	3	2	7

Reporting group values	Arm #4	Arm #5A	Arm #5B
Number of subjects	4	8	6
Age categorical Units: Subjects			
Adults (18-64 years)	1	5	3
From 65-84 years	3	3	3
Gender categorical Units: Subjects			
Female	0	3	2
Male	4	5	4

Reporting group values	Total		
Number of subjects	41		

Age categorical Units: Subjects			
Adults (18-64 years)	25		
From 65-84 years	16		
Gender categorical Units: Subjects			
Female	16		
Male	25		

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects receiving at least one dose VB10.NEO

Reporting group values	Safety analysis set		
Number of subjects	41		
Age categorical Units: Subjects			
Adults (18-64 years)	25		
From 65-84 years	16		
Gender categorical Units: Subjects			
Female	16		
Male	25		

End points

End points reporting groups

Reporting group title	Arm #1
Reporting group description: Melanoma	
Reporting group title	Arm #2
Reporting group description: NSCLC	
Reporting group title	Arm #3
Reporting group description: RCC	
Reporting group title	Arm #4
Reporting group description: Urothelial	
Reporting group title	Arm #5A
Reporting group description: SCCHN	
Reporting group title	Arm #5B
Reporting group description: SCCHN VB10.NEO and NKTR-214	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects receiving at least one dose VB10.NEO	

Primary: Number of patients with treatment emergent adverse events

End point title	Number of patients with treatment emergent adverse events[1]
End point description: A TEAE was defined as any AE that had an onset on or after the date of first vaccination or any preexisting condition that had worsened on or after the date of first vaccination. If it could not be determined whether the AE was treatment-emergent due to a partial onset date, it was counted as treatment-emergent.	
End point type	Primary
End point timeframe: From first VB10.NEO vaccination to 30 days after last VB10.NEO vaccination	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a safety endpoint and no statistical analysis was performed.

End point values	Arm #1	Arm #2	Arm #3	Arm #4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	5	10	4
Units: Patients with events	8	5	9	4

End point values	Arm #5A	Arm #5B	Safety analysis set	

Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	8	6	41	
Units: Patients with events	8	6	40	

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with TEAEs leading to treatment discontinuation

End point title	Number of patients with TEAEs leading to treatment discontinuation[2]

End point description:

A TEAE leading to treatment discontinuation was defined as any TEAE where the outcome was registered as treatment discontinuation.

End point type	Primary

End point timeframe:

From first VB10.NEO vaccination to 30 days after last VB10.NEO vaccination

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: This is a safety endpoint and no statistical analysis was performed.

End point values	Arm #1	Arm #2	Arm #3	Arm #4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	5	10	4
Units: Number of patients	1	1	0	1

End point values	Arm #5A	Arm #5B	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	8	6	41	
Units: Number of patients	2	1	6	

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with TEAEs ≥grade 3 according to CTCAE

End point title	Number of patients with TEAEs ≥grade 3 according to CTCAE[3]

End point description:

All AEs were graded 1-5 according to the CTCAE grading system.

End point type	Primary

End point timeframe:

From first VB10.NEO vaccination to 30 days after last VB10.NEO vaccination

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a safety endpoint and no statistical analysis was performed.

End point values	Arm #1	Arm #2	Arm #3	Arm #4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	5	10	4
Units: Number of patients	4	2	3	4

End point values	Arm #5A	Arm #5B	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	8	6	41	
Units: Number of patients	7	4	24	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first VB10.NEO vaccination to 30 days after last VB10.NEO vaccination	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0
Reporting groups	
Reporting group title	Arm #1
Reporting group description: Melanoma	
Reporting group title	Arm #3
Reporting group description: RCC	
Reporting group title	Arm #2
Reporting group description: NSCLC	
Reporting group title	Arm #4
Reporting group description: Urothelial	
Reporting group title	Arm #5A
Reporting group description: SCCHN	
Reporting group title	Arm #5B
Reporting group description: SCCHN VB10.NEO and NKTR-214	
Reporting group title	Total
Reporting group description: Pool of all patients	

Serious adverse events	Arm #1	Arm #3	Arm #2
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	2 / 10 (20.00%)	3 / 5 (60.00%)
number of deaths (all causes)	2	5	3
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Surgical and medical procedures			

Postoperative care			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Routine health maintenance			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchostenosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated lung disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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

Ileus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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			
Biopsy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Panendoscopy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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			
Procedural haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation skin injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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			
Atrioventricular block complete			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Epilepsy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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			
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Subileus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (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
Autoimmune colitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Cholestasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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			
Osteonecrosis of jaw			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess neck			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Arthritis bacterial			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
COVID-19			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Erysipelas			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Herpes zoster			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (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 device infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (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

Serious adverse events	Arm #4	Arm #5A	Arm #5B
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	7 / 8 (87.50%)	3 / 6 (50.00%)
number of deaths (all causes)	2	3	1
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Surgical and medical procedures			
Postoperative care			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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
Routine health maintenance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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			
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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
Bronchostenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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 exertional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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
Immune-mediated lung disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (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

Pulmonary embolism			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (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
Ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Biopsy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (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
Panendoscopy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (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
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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
Radiation skin injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block complete			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (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
Epilepsy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (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
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (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
Blood and lymphatic system disorders			
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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			
Subileus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (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

Autoimmune colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (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
Cholestasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess neck			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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
COVID-19			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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
Herpes zoster			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (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
Infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (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	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 41 (56.10%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	3		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Postoperative care			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Routine health maintenance			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bronchostenosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Immune-mediated lung disease			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Biopsy			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Panendoscopy			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation skin injury			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pain			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Subileus			

subjects affected / exposed	2 / 41 (4.88%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Autoimmune colitis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteonecrosis of jaw				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	3 / 41 (7.32%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Abscess neck				

subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Erysipelas				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Arm #1	Arm #3	Arm #2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	9 / 10 (90.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Papilloma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Squamous cell carcinoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	3 / 10 (30.00%)	0 / 5 (0.00%)
occurrences (all)	0	14	0
Aneurysm arteriovenous			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Deep vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Peripheral venous disease			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cancer surgery			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	4 / 10 (40.00%)	2 / 5 (40.00%)
occurrences (all)	0	5	2
Pyrexia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	4	1	1
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Condition aggravated			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	4	1
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injection site haematoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Adverse reaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Generalised oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Injection site bruising			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injection site erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Adverse drug reaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infusion site pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Genital rash			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pelvic pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Scrotal dermatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Epistaxis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Bronchostenosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Immune-mediated lung disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pulmonary pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rhonchi			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Stridor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Throat tightness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Agitation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Conversion disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Delirium			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 8 (25.00%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	2	6	1
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 8 (37.50%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	4	1	1
Lipase increased			
subjects affected / exposed	3 / 8 (37.50%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	4	1	1
C-reactive protein increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Gamma-glutamyltra nsferase increased			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	3	2	0
Weight decreased			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Amylase increased			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 8 (37.50%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	4	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Blood albumin decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood creatine increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Protein total increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
White blood cell count increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Facial bones fracture			

subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Immunisation reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Radiation skin injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Synovial rupture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Atrioventricular block complete			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Bundle branch block right			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Polyneuropathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ageusia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dysaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Facial paresis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Fine motor skill dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Monoparesis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Post herpetic neuralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Seizure			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 8 (37.50%)	1 / 10 (10.00%)	2 / 5 (40.00%)
occurrences (all)	4	1	4
Lymphopenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Eosinophilia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Leukocytosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Lymph node pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Neutrophilia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Ear haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Chalazion			

subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Entropion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	3 / 10 (30.00%)	3 / 5 (60.00%)
occurrences (all)	2	3	3
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	2	1	1
Vomiting			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	2 / 5 (40.00%)
occurrences (all)	3	1	2
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Dry mouth			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Food poisoning			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Oral disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Subileus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Abdominal pain lower			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Angular cheilitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ascites			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Enteritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Swollen tongue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tongue erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Immune-mediated hepatitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	4	1
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Intertrigo			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Keratosis pilaris			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Night sweats			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Rash erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Skin toxicity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal impairment			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Acute kidney injury			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Hypothyroidism			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Thyroid mass			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	2 / 5 (40.00%)
occurrences (all)	0	3	2
Back pain			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Arthritis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Flank pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			

subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain in jaw			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Immune-mediated arthritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 8 (25.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	3	1	1
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	2
Infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Arthritis bacterial			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Tinea infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tinea pedis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Wound infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Hypoalbuminaemia			
subjects affected / exposed	3 / 8 (37.50%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	5	0	0
Hyponatraemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Iron deficiency			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Calcium deficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Magnesium deficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vitamin K deficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Arm #4	Arm #5A	Arm #5B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	8 / 8 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Papilloma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Squamous cell carcinoma			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 4 (50.00%)	3 / 8 (37.50%)	1 / 6 (16.67%)
occurrences (all)	10	8	8
Aneurysm arteriovenous			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Deep vein thrombosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	4
Peripheral venous disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cancer surgery			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	4 / 8 (50.00%)	3 / 6 (50.00%)
occurrences (all)	1	4	6
Pyrexia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	2 / 6 (33.33%)
occurrences (all)	0	1	4
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Pain			
subjects affected / exposed	2 / 4 (50.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Chills			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Condition aggravated			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
General physical health deterioration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Injection site haematoma			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Adverse reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Asthenia			

subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Generalised oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Impaired healing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Injection site reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injection site swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Adverse drug reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infusion site pruritus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oedema			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Genital rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Scrotal dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			

subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Bronchostenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Immune-mediated lung disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Laryngeal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	4
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pulmonary pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhonchi			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Stridor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Throat tightness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Wheezing			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Agitation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conversion disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Lipase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
C-reactive protein increased			

subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	2 / 6 (33.33%)
occurrences (all)	1	2	3
Gamma-glutamyltra nsferase increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Amylase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood albumin decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lymphocyte count decreased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Protein total increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
White blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Facial bones fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Immunisation reaction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Radiation skin injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Synovial rupture			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Atrioventricular block complete			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bundle branch block right			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Polyneuropathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Ageusia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Dysaesthesia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Facial paresis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fine motor skill dysfunction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Monoparesis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Post herpetic neuralgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Lymphopenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Eosinophilia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Leukocytosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Lymph node pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophilia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chalazion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Entropion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	3 / 8 (37.50%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	2 / 8 (25.00%)	2 / 6 (33.33%)
occurrences (all)	1	3	3
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	2 / 6 (33.33%)
occurrences (all)	1	1	3
Abdominal pain			

subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Food poisoning			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oral disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Subileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Abdominal pain lower			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Angular cheilitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Constipation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Enteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Swollen tongue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tongue erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Immune-mediated hepatitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	4 / 6 (66.67%)
occurrences (all)	0	0	5
Erythema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	5
Decubitus ulcer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Rash maculo-papular			

subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Intertrigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Keratosis pilaris			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Skin disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Skin fissures			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin toxicity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	3 / 6 (50.00%)
occurrences (all)	0	1	4
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	2 / 4 (50.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Haematuria			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Renal impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Thyroid mass			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain in jaw			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Bone pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Immune-mediated arthritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Osteonecrosis of jaw			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 4 (75.00%)	2 / 8 (25.00%)	0 / 6 (0.00%)
occurrences (all)	4	6	0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 4 (0.00%)	3 / 8 (37.50%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Arthritis bacterial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Diverticulitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis bacterial			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gingivitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Oral herpes			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tinea infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tinea pedis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Wound infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	8	1

Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Calcium deficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Magnesium deficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vitamin K deficiency			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 41 (97.56%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Papilloma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Squamous cell carcinoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Tumour pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	40		
Aneurysm arteriovenous			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Deep vein thrombosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypotension			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	4		
Peripheral venous disease			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Cancer surgery			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 41 (34.15%)		
occurrences (all)	18		
Pyrexia			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	11		
Mucosal inflammation			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	5		
Condition aggravated			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	4		
General physical health deterioration			

subjects affected / exposed	2 / 41 (4.88%)			
occurrences (all)	2			
Influenza like illness				
subjects affected / exposed	2 / 41 (4.88%)			
occurrences (all)	3			
Injection site haematoma				
subjects affected / exposed	2 / 41 (4.88%)			
occurrences (all)	2			
Malaise				
subjects affected / exposed	2 / 41 (4.88%)			
occurrences (all)	2			
Oedema peripheral				
subjects affected / exposed	2 / 41 (4.88%)			
occurrences (all)	2			
Adverse reaction				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Asthenia				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Face oedema				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Generalised oedema				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Impaired healing				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Injection site bruising				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Injection site erythema				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	3			
Injection site reaction				

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Injection site swelling			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Swelling			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Adverse drug reaction			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Infusion site pruritus			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Genital rash			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pelvic pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Scrotal dermatitis			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Pleural effusion			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Pulmonary embolism			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Bronchostenosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Immune-mediated lung disease			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Laryngeal inflammation			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pulmonary pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Rhonchi			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Stridor			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Throat tightness			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Agitation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

Conversion disorder subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Delirium subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Insomnia subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 12		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 9		
Lipase increased subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 8		
C-reactive protein increased subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 8		
Gamma-glutamyltra nsferase increased subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 7		
Weight decreased subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 5		
Amylase increased subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 5		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 5		
Blood creatinine increased			

subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	5		
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Blood albumin decreased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood creatine increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Protein total increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Facial bones fracture			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Fracture			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Immunisation reaction			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Radiation skin injury			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Synovial rupture			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Atrioventricular block complete			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Bundle branch block right			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Tachycardia			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Polyneuropathy			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Syncope			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Ageusia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Dysaesthesia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Facial paresis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Fine motor skill dysfunction			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Monoparesis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

Post herpetic neuralgia subjects affected / exposed occurrences (all) Seizure subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1 1 / 41 (2.44%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Eosinophilia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Lymph node pain subjects affected / exposed occurrences (all) Lymphadenopathy subjects affected / exposed occurrences (all) Neutrophilia subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 11 3 / 41 (7.32%) 5 2 / 41 (4.88%) 3 1 / 41 (2.44%) 1 1 / 41 (2.44%) 1 1 / 41 (2.44%) 2 1 / 41 (2.44%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) Ear haemorrhage subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2 1 / 41 (2.44%) 1		
Eye disorders			

Cataract			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Chalazion			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Entropion			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 41 (26.83%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	11		
Vomiting			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	11		
Abdominal pain			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Food poisoning			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Oral disorder			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Subileus			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Abdominal pain lower			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Angular cheilitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Enteritis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Swollen tongue			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Tongue erythema			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hepatobiliary disorders			

Hepatitis			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Immune-mediated hepatitis			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	10		
Erythema			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	7		
Decubitus ulcer			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Rash maculo-papular			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Skin lesion			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Intertrigo			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Keratosis pilaris			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Rash erythematous			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	3		
Skin disorder			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Skin exfoliation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Skin toxicity			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	6		
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Haematuria			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Renal impairment			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Acute kidney injury			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Hypothyroidism			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Thyroid mass			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	9		
Back pain			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Arthritis			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Myalgia			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Pain in jaw			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Immune-mediated arthritis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	15		
Pneumonia			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	3		
Infection			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		

Nasopharyngitis				
subjects affected / exposed	4 / 41 (9.76%)			
occurrences (all)	4			
Urinary tract infection bacterial				
subjects affected / exposed	2 / 41 (4.88%)			
occurrences (all)	2			
Arthritis bacterial				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	2			
Diverticulitis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Gastroenteritis bacterial				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Gastrointestinal infection				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Gingivitis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Herpes zoster				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	2			
Oral herpes				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Otitis media				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences (all)	1			

Tinea infection subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Tinea pedis subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Wound infection subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		
Hypocalcaemia subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		
Hypokalaemia subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 11		
Dehydration subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Hyperkalaemia subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 4		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 5		
Hyponatraemia subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2		
Iron deficiency			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Calcium deficiency			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Magnesium deficiency			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Vitamin K deficiency			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2018	The amendments in the protocol include the increase in the number of biopsies from 2 to 5 and the possibility of carrying out CT-guided biopsies, amongst others. The additional biopsies support the investigation of the mutagenic properties, the immunological activity and the clinical efficacy and make it possible to carry out the descriptive analyses outlined in the protocol. CT-guided biopsies replace a major surgical procedure, e.g., in the case of tumours located deep inside the body and make it possible to secure high-quality samples with sufficient tumour cell content. The investigator will decide at each visit which tumour lesions will be chosen for each patient and whether CT-guided biopsies are required.
13 March 2019	To account for poor clinical outcomes and short overall survival times for patients with squamous cell carcinoma of the head and neck (SCCHN), it was decided to improve the conditions of inclusion criteria of these patients to the trial. Inclusion Criteria were updated to state that SCCHN patient must be on CPI and removed the condition of "for at least 12 weeks". In collaboration with Nektar Therapeutics, a possible synergistic effect of VB10.NEO with bempegaldesleukin (NKTR-214) was tested in pre-clinical studies. Based on strong non-clinical data, it was decided to make NKTR-214 available to SCCHN patients in this clinical trial. As such, a new treatment arm (arm 5B) for SCCHN was created for these patients to investigate the combination of VB10.NEO with bempegaldesleukin in patients with SCCHN. To facilitate overall recruitment and increase the enrollment of SCCHN patients the number of study centers was increase from 3 to 4-8 centers. To increase the chances of patients consenting to follow-up biopsies, the total number of biopsies that can be taken per visit (all arms) has been reduced from 5 to 3. To analyse changes in the tumour microenvironment specifically related to the introduction of NKTR-214, new time points for collecting biopsies were included in arm 5B. Further, to allow inter-patient comparison, the biopsies were also included in arm 5A.
15 May 2019	The study protocol has been revised to include monthly checks on blood values in the 5B cohort, once treatment with bempegaldesleukin has begun.
05 December 2019	The decision to investigate any possible relationships between clinical responses and changes in the frequencies and repertoire of tumour-specific mutations identified in the cell-free DNA (cfDNA), with a particular focus on the neoepitopes targeted by VB10.NEO. Tumour heterogeneity may lead to different neoepitope expression patterns in different lesions in metastatic patients. Therefore, additional samples will be collected at screening and used for the neoepitope selection process to identify the optimal neoepitopes. Inclusion criteria for patients with melanoma have changed. This change is based on the decision to improve the conditions to enroll patients with melanoma in this trial. The waiting time from the start of CPI treatment (as standard of care) to the first dose of the IMP VB10.NEO will be shortened by dropping the requirement that CPI must have been given for at least 12 weeks at screening. Now, melanoma patients must be on CPI at screening. Standard of care (SoC) for the target population in the study have evolved since the initial submission of this study, and CPIs (anti PD-1 and anti PD-L1) are more commonly used as part of SoC in combination with other anti-cancer therapies. The patients in this trial will be on CPI treatment as part of their SoC. Combinations of anti-PD-1 and anti-PD-L1 with an anti-CTLA-4 agent or other anticancer therapies are allowed now if considered required at the investigator's discretion.

07 April 2020	Safety update was based on clinical safety data as of 28 February 2020 and reflects the updates included in the VB10.NEO Investigator's Brochure. Safety update reflects the updates in the bempegaldesleukin Investigator's Brochure edition 8.0, release date 25 March 2020. Total potential number of patients are increased from 50 to 60 patients to allow up to 10 patients starting treatment in each of the 6 treatment arms. Adding information that recruitment can be halted or slowed down at times to adapt to manufacturing capacity in order to avoid over-recruitment of patients that might result in delays of vaccine supply. Decision to change the post vaccination observation period of 24 h after first dose to 4 h, and 2 h for subsequent vaccinations. Clarification on how to handle vaccination delays in case a vaccination needs to be postponed. Addition of follow-up visits 3 and 6 months after end of treatment including addition of blood sampling for peripheral T cell response (PBMCs) at all follow-up visits to investigate the long-term efficacy of VB10.NEO after completion or discontinuation of treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 February 2020	Investigators in the VB N-01 trial were informed about a temporary pause in the recruitment. The reason for the pause was constraints in the supply chain which lead to a backlog and an increased manufacturing time > 16 weeks.	03 March 2020

Notes:

Limitations and caveats

None reported