Clinical trial results:
A Phase I/II Study of SEL24 in Patients with Acute Myeloid Leukemia

Summary

EudraCT number	2019-000941-10
Trial protocol	PL ES IT
Global end of trial date	13 April 2023

Results information

Result version number	v1 (current)
This version publication date	04 January 2025
First version publication date	04 January 2025

Trial information

Trial identification

Sponsor protocol code	CLI24-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03008187
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A
Sponsor organisation address	10, Via Tito Speri, Pomezia, Italy, 00071
Public contact	Angela Capriati, Menarini Ricerche S.p.A, +39 0555680 9990,
Scientific contact	Angela Capriati, Menarini Ricerche S.p.A, +39 0555680 9990,

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	13 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the safety profile and determine the recommended dose of single agent MEN1703 (SEL24).

Protection of trial subjects:

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the participants shall remain protected in accordance with the Laws and Regulation on personal data protection from time to time applicable such as the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014 or the US Health Insurance Portability and Accountability Act regulations (HIPAA), the US Common Rule (45 CFR 46.116).

The study protocol defines the appropriate technical and organisational measures that shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfilment of participants' privacy rights.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Italy: 17
Worldwide total number of subjects	73
EEA total number of subjects	43

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	23
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial examined 6 different doses of MEN1703: 25 milligrams (mg); 50 mg; 75 mg; 100 mg; 125 mg; 150 mg.

Pre-assignment

Screening details:

Participants were screened across 4 countries: Unites States, Italy, Spain, and Poland.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (25 mg)

Arm description:

Participants received MEN1703 (25 mg) orally once daily for 14 consecutive days in cycles of 21 days.

Arm type	Experimental
Investigational medicinal product name	MEN1703
Investigational medicinal product code	
Other name	SEL24-B489, SEL24
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MEN1703 (25 mg) was administered orally once daily for 14 consecutive days in cycles of 21 days.

Arm title	Cohort 2 (50 mg)

Arm description:

Participants received MEN1703 (50 mg) orally once daily for 14 consecutive days in cycles of 21 days.

Arm type	Experimental
Investigational medicinal product name	MEN1703
Investigational medicinal product code	
Other name	SEL24-B489, SEL24
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MEN1703 (50 mg) was administered orally once daily for 14 consecutive days in cycles of 21 days.

Arm title	Cohort 3 (75 mg)

Arm description:

Participants received MEN1703 (75 mg) orally once daily for 14 consecutive days in cycles of 21 days.

Arm type	Experimental
Investigational medicinal product name	MEN1703
Investigational medicinal product code	
Other name	SEL24-B489, SEL24
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
MEN1703 (75 mg) was administered orally once daily for 14 consecutive days in cycles of 21 days.

Arm title	Cohort 4 (100 mg)
Arm description:	
Participants received MEN1703 (100 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Arm type	Experimental
Investigational medicinal product name	MEN1703
Investigational medicinal product code	
Other name	SEL24-B489, SEL24
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
MEN1703 (100 mg) was administered orally once daily for 14 consecutive days in cycles of 21 days.	
Arm title	Cohort 5 (125 mg)
Arm description:	
Participants received MEN1703 (125 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Arm type	Experimental
Investigational medicinal product name	MEN1703
Investigational medicinal product code	
Other name	SEL24-B489, SEL24
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
MEN1703 (125 mg) was administered orally once daily for 14 consecutive days in cycles of 21 days.	
Arm title	Cohort 6 (150 mg)
Arm description:	
Participants received MEN1703 (150 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Arm type	Experimental
Investigational medicinal product name	MEN1703
Investigational medicinal product code	
Other name	SEL24-B489, SEL24
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
MEN1703 (150 mg) was administered orally once daily for 14 consecutive days in cycles of 21 days.	

Number of subjects in period 1	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)
Started	2	3	3
Received at Least 1 Dose of Study Drug	2	3	3
Completed	2	3	3

Joined	0	0	0

Participants enrolled into Part 2 (Dose Expansion)	-	-	-

Number of subjects in period 1	Cohort 4 (100 mg)	Cohort 5 (125 mg)	Cohort 6 (150 mg)
Started	6	7	4
Received at Least 1 Dose of Study Drug	6	55	4
Completed	6	55	4

Joined	0	48	0
Participants enrolled into Part 2 (Dose Expansion)	-	48	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (25 mg)
Reporting group description:	
Participants received MEN1703 (25 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 2 (50 mg)
Reporting group description:	
Participants received MEN1703 (50 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 3 (75 mg)
Reporting group description:	
Participants received MEN1703 (75 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 4 (100 mg)
Reporting group description:	
Participants received MEN1703 (100 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 5 (125 mg)
Reporting group description:	
Participants received MEN1703 (125 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 6 (150 mg)
Reporting group description:	
Participants received MEN1703 (150 mg) orally once daily for 14 consecutive days in cycles of 21 days.	

Reporting group values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)
Number of subjects	2	3	3
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	47.50	71.00	75.33
standard deviation	± 31.820	± 5.000	± 8.963
Gender categorical Units: Subjects			
Female	1	2	2
Male	1	1	1
Race			
United States National Institutes of Health and Office of Management and Budget (NIH/OMB) Classification Categories			
Units: Subjects			
American Indian or Alaska Native	0	0	0

Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	1	3	3
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity			
NIH/OMB Classification Categories			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	2	3	3
Unknown or Not Reported	0	0	0

Reporting group values	Cohort 4 (100 mg)	Cohort 5 (125 mg)	Cohort 6 (150 mg)
Number of subjects	6	55	4
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	65.67	65.55	63.50
standard deviation	± 18.726	± 12.060	± 7.047
Gender categorical			
Units: Subjects			
Female	3	24	1
Male	3	31	3
Race			
United States National Institutes of Health and Office of Management and Budget (NIH/OMB) Classification Categories			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	0
White	4	51	4
More than one race	0	0	0
Unknown or Not Reported	0	2	0
Ethnicity			
NIH/OMB Classification Categories			
Units: Subjects			
Hispanic or Latino	0	2	0

Not Hispanic or Latino	6	53	4
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	73		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	--		
Gender categorical Units: Subjects			
Female	33		
Male	40		
Race			
United States National Institutes of Health and Office of Management and Budget (NIH/OMB) Classification Categories			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	4		
White	66		
More than one race	0		
Unknown or Not Reported	2		
Ethnicity			
NIH/OMB Classification Categories			
Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	71		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Cohort 1 (25 mg)
Reporting group description:	
Participants received MEN1703 (25 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 2 (50 mg)
Reporting group description:	
Participants received MEN1703 (50 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 3 (75 mg)
Reporting group description:	
Participants received MEN1703 (75 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 4 (100 mg)
Reporting group description:	
Participants received MEN1703 (100 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 5 (125 mg)
Reporting group description:	
Participants received MEN1703 (125 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 6 (150 mg)
Reporting group description:	
Participants received MEN1703 (150 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants that received at least 1 dose of MEN1703.	

Subject analysis set title	Pharmacokinetics (PK) Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who received any dose of MEN1703 and had at least 1 measurable drug concentration.	
Subject analysis set title	Efficacy Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants in each cohort that have completed 1 cycle of treatment (considering both the treatment and the washout period) and have taken at least 75% of the study drug during the first cycle.	

Subject analysis set title	Bone Marrow Assessment
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
A sub-group of participants from every cohort from the Safety Population with available baseline bone marrow assessment and at least 1 post-baseline bone marrow assessment.	

Primary: Part 1: Number of Participants Experiencing Dose-limiting Toxicity (DLT)

End point title	Part 1: Number of Participants Experiencing Dose-limiting Toxicity (DLT)[1]
End point description:	
AEs were graded according to the National Cancer Institute common terminology criteria for adverse events, version 4.03. The following AEs were considered as DLT unless they were clearly and incontrovertibly attributable to the underlying disease or to an extraneous cause: Grade 5 toxicity; Grade 4 neutropenia lasting ≥42 days from the start of the therapy cycle in absence of evidence of active acute myeloid leukemia (AML) (<5% blasts); Grade 3 or 4 non-hematologic toxicity (with protocol-define exceptions). Only clinically significant abnormalities in laboratory findings, physical examination, vital signs, weight or electrocardiogram were considered for DLT assessment. Here, 'Number of subjects analyzed' signifies those participants from Part 1 who were evaluable for this end	

point.

End point type	Primary

End point timeframe:

Day 1 through Day 21 (first treatment cycle)

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: Only descriptive statistics (number of participants) are reported for this primary end point, as prespecified in the statistical analysis plan.

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[2]	3[3]	3[4]	6[5]
Units: Participants	1	0	0	0

Notes:

[2] - Safety Population

[3] - Safety Population

[4] - Safety Population

[5] - Safety Population

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[6]	4[7]		
Units: Participants	1	3		

Notes:

[6] - Safety Population

[7] - Safety Population

Statistical analyses

No statistical analyses for this end point

Primary: Part 1 and Part 2: Number of Participants Experiencing Treatment-emergent Adverse Events

End point title	Part 1 and Part 2: Number of Participants Experiencing Treatment-emergent Adverse Events[8]

End point description:

An adverse event (AE) was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a participant or clinical investigation participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational medicinal product. A summary of serious and all other non-serious adverse events regardless of causality is located in the Reported Adverse events module.

End point type	Primary

End point timeframe:

Up to 21 months

Notes:

[8] - 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: Only descriptive statistics (number of participants) are reported for this primary end point, as prespecified in the statistical analysis plan.

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[9]	3[10]	3[11]	6[12]
Units: Participants	2	3	3	6

Notes:

[9] - Safety Population

[10] - Safety Population

[11] - Safety Population

[12] - Safety Population

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[13]	4[14]		
Units: Participants	54	4		

Notes:

[13] - Safety Population

[14] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Overall Response Rate (ORR)

End point title	Part 1 and Part 2: Overall Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants who had a complete remission (CR), complete remission with incomplete hematologic recovery (CRi), complete remission with partial hematologic recovery (CRh), or morphologic leukemia-free state (MLFS) response to therapy. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Up to 32 Months

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[15]	3[16]	3[17]	6[18]
Units: percentage of participants				
number (not applicable)				
Efficacy Population	0	0	50.0	0

Notes:

[15] - Efficacy Population (N=0)

[16] - Efficacy Population (N=1)

[17] - Efficacy Population (N=2)

[18] - Efficacy Population (N=4)

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[19]	4[20]		
Units: percentage of participants				
number (not applicable)				
Efficacy Population	13.5	0		

Notes:

[19] - Efficacy Population (N=37)

[20] - Efficacy Population (N=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Partial Remission (PR) Rate

End point title	Part 1 and Part 2: Partial Remission (PR) Rate

End point description:

PR rate was defined as the percentage of participants who had a partial remission response to therapy. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[21]	3[22]	3[23]	6[24]
Units: Percentage of Participants				
number (not applicable)				
Efficacy Population	0	0	0	0

Notes:

[21] - Efficacy Population (N=0)

[22] - Efficacy Population (N=1)

[23] - Efficacy Population (N=2)

[24] - Efficacy Population (N=4)

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[25]	4[26]		
Units: Percentage of Participants				
number (not applicable)				
Efficacy Population	0	0		

Notes:

[25] - Efficacy Population (N=37)

[26] - Efficacy Population (N=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Duration of Response (DoR)

End point title	Part 1 and Part 2: Duration of Response (DoR)

End point description:

DoR was defined as the time from the date of first CR, CRi, CRh, CR without minimal residual disease (CRMRD-), MLFS or PR until the date of documented relapse of any type, progressive disease or death due to disease progression for participants who achieve CR, CRi, CRh, CRMRD-, MLFS or PR. Results are reported in days. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point. '9999'=values were non-estimable (insufficient number of participants with events).

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[27]	3[28]	3[29]	6[30]
Units: Days				
median (confidence interval 95%)				
Efficacy Population	9999 (9999 to 9999)	9999 (9999 to 9999)	79.0 (0 to 9999)	9999 (9999 to 9999)

Notes:

[27] - Efficacy Population (N=0)

[28] - Efficacy Population (N=1)

[29] - Efficacy Population (N=2)

[30] - Efficacy Population (N=4)

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[31]	4[32]		
Units: Days				
median (confidence interval 95%)				
Efficacy Population	63.0 (44.0 to 9999)	9999 (9999 to 9999)		

Notes:

[31] - Efficacy Population (N=37)

[32] - Efficacy Population (N=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Relapse Free Survival (RFS)

End point title	Part 1 and Part 2: Relapse Free Survival (RFS)

End point description:

RFS was defined as the time from the date of first CR, CRi, CRh or CRMRD- until the date of documented relapse or death from any cause. Results are reported in days. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point. '9999'=values were non-estimable (insufficient number of participants with events).

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[33]	3[34]	3[35]	6[36]
Units: Days				
median (confidence interval 95%)				
Efficacy Population	9999 (9999 to 9999)	9999 (9999 to 9999)	81.0 (0 to 9999)	9999 (9999 to 9999)

Notes:

[33] - Efficacy Population (N=0)

[34] - Efficacy Population (N=1)

[35] - Efficacy Population (N=2)

[36] - Efficacy Population (N=4)

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[37]	4[38]		
Units: Days				
median (confidence interval 95%)				
Efficacy Population	64.0 (44.0 to 9999)	9999 (9999 to 9999)		

Notes:

[37] - Efficacy Population (N=37)

[38] - Efficacy Population (N=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Event Free Survival (EFS)

End point title	Part 1 and Part 2: Event Free Survival (EFS)

End point description:

EFS was defined as the time from the date of first study drug intake until the date of documented relapse, treatment failure, or death from any cause. Results are reported in days. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point. '9999'=values were non-estimable (insufficient number of participants with events).

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[39]	3[40]	3[41]	6
Units: Days				
median (confidence interval 95%)				

Efficacy Population	9999 (0 to 9999)	15.0 (0 to 9999)	14.0 (0 to 9999)	14.0 (14.0 to 9999)

Notes:

[39] - Efficacy Population (N=0)

[40] - Efficacy Population (N=2)

[41] - Efficacy Population (N=4)

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[42]	4[43]		
Units: Days				
median (confidence interval 95%)				
Efficacy Population	43.0 (42.0 to 49.0)	15.0 (14.0 to 9999)		

Notes:

[42] - Efficacy Population (N=37)

[43] - Efficacy Population (N=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Overall Survival (OS)

End point title	Part 1 and Part 2: Overall Survival (OS)

End point description:

OS was defined as the number of days between the first study drug administration and death from any cause. Results are reported in days. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point. '9999'=values were non-estimable (insufficient number of participants with events).

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[44]	3[45]	3[46]	6[47]
Units: Days				
median (confidence interval 95%)				
Safety Population	85.5 (48.0 to 9999)	127.0 (43.0 to 9999)	91.0 (63.0 to 9999)	9999 (108.0 to 9999)
Efficacy Population	9999 (9999 to 9999)	43.0 (0 to 9999)	138.5 (63.0 to 9999)	9999 (108.0 to 9999)

Notes:

[44] - Safety Population (N=2); Efficacy Population (N=0)

[45] - Safety Population (N=3); Efficacy Population (N=1)

[46] - Safety Population (N=3); Efficacy Population (N=2)

[47] - Safety Population (N=6); Efficacy Population (N=4)

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[48]	4[49]		
Units: Days				
median (confidence interval 95%)				
Safety Population	84.0 (49.0 to 185.0)	42.5 (8.0 to 9999)		
Efficacy Population	144.0 (72.0 to 287.0)	42.5 (34.0 to 9999)		

Notes:

[48] - Safety Population (N=55); Efficacy Population (N=37)

[49] - Safety Population (N=4); Efficacy Population (N=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Transfusion Conversion Rate

End point title	Part 1 and Part 2: Transfusion Conversion Rate[50]

End point description:

Transfusion conversion rate was defined as the percentage of participants who were transfusion dependent at baseline period but became transfusion independent at post-baseline. Participants were classified as baseline transfusion independent if there were no red blood cells (RBC) or platelet transfusions at baseline; otherwise, the participant was considered as baseline transfusion dependent. Participants were classified post-baseline transfusion independent in the event of 56 consecutive days without any RBC or platelet transfusion post-baseline; otherwise, the participant was considered post-baseline transfusion dependent. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Up to 21 Months

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected only for Cohort 5 for this end point as pre-specified in the protocol.

End point values	Cohort 5 (125 mg)			
Subject group type	Reporting group			
Number of subjects analysed	55[51]			
Units: Percentage of Participants				
number (not applicable)				
Efficacy Population	25			

Notes:

[51] - Efficacy Population (N=4)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) Rate

End point title	Part 1 and Part 2: Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) Rate[52]

End point description:

Allogeneic HSCT rate was defined as the percentage of participants undergoing allogeneic stem cell transplant during the study period. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Up to 21 Months

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected only for Cohort 5 for this end point as pre-specified in the protocol.

End point values	Cohort 5 (125 mg)			
Subject group type	Reporting group			
Number of subjects analysed	55[53]			
Units: Percentage of Participants				
number (not applicable)				
Efficacy Population	2.7			

Notes:

[53] - Efficacy Population (N=37)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Percentage of Participants with ≥ 50% Bone Marrow Blast Reduction

End point title	Part 1 and Part 2: Percentage of Participants with ≥ 50% Bone Marrow Blast Reduction

End point description:

Bone marrow aspirates/biopsies were taken at designated timepoints for evaluation of leukemic blast proportion in the bone marrow. A reduction in bone marrow blast proportion indicates increased antileukemic activity of the study drug. Here, 'Number of subjects analyzed' signifies those participants from all cohorts who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Up to 20 Months

End point values	Bone Marrow Assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: Percentage of Participants				
number (not applicable)	24.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Transfusion Maintenance Rate

End point title	Part 1 and Part 2: Transfusion Maintenance Rate[54]

End point description:

Transfusion maintenance rate was defined as the percentage of participants who were transfusion independent at baseline period and still maintained to be transfusion independent at post-baseline. Participants were classified as baseline transfusion independent if there were no RBC or platelet transfusions at baseline; otherwise, the participant was considered as baseline transfusion dependent. Participants were classified post-baseline transfusion independent in the event of 56 consecutive days without any RBC or platelet transfusion post-baseline; otherwise, the participant was considered post-baseline transfusion dependent. Here, 'Number of subjects analyzed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Up to 21 months

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected only for Cohort 5 for this end point as pre-specified in the protocol.

End point values	Cohort 5 (125 mg)			
Subject group type	Reporting group			
Number of subjects analysed	55[55]			
Units: Percentage of Participants				
number (not applicable)				
Efficacy Population	100			

Notes:

[55] - Efficacy Population (N=2)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Maximum Observed Concentration (Cmax) for MEN1703

End point title	Part 1 and Part 2: Maximum Observed Concentration (Cmax) for MEN1703

End point description:

Nominal blood samples were taken at designated timepoints for evaluation of concentration levels of MEN1703 in plasma. Results are reported as nanograms/millilitre (ng/mL). Standard error not reported (0000), arithmetic coefficient of variation (CV%) reported instead. '9999'=values were non-estimable (insufficient number of participants with events). Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point at the specified time points.

End point type	Secondary

End point timeframe:

Day 1 and Day 14 of Cycle 1 (pre-dose, up to 120 hours post dose) (21 days/cycle)

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[56]	3[57]	3[58]	6[59]
Units: ng/mL				
arithmetic mean (standard error)				
Cycle 1 Day 1	8.77 (± 0000)	33.58 (± 0000)	60.55 (± 0000)	73.25 (± 0000)
Cycle 1 Day 14	9999 (± 9999)	74.32 (± 0000)	167.08 (± 0000)	294.25 (± 0000)

Notes:

[56] - PK Population: Cycle 1 Day 1 (N=2), CV% = 29.3; Cycle 1 Day 14 (N=0)

[57] - PK Population: Cycle 1 Day 1 (N=3), CV% = 33.5; Cycle 1 Day 14 (N=3) CV% = 64.1

[58] - PK Population: Cycle 1 Day 1 (N=3), CV% = 88.3; Cycle 1 Day 14 (N=3) CV% = 60.9

[59] - PK Population: Cycle 1 Day 1 (N=6), CV% = 50.4; Cycle 1 Day 14 (N=6) CV% = 53.5

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[60]	4[61]		
Units: ng/mL				
arithmetic mean (standard error)				
Cycle 1 Day 1	152.94 (± 0000)	249.00 (± 0000)		
Cycle 1 Day 14	507.18 (± 0000)	759.36 (± 0000)		

Notes:

[60] - PK Population: Cycle 1 Day 1 (N=55), CV% = 54; Cycle 1 Day 14 (N=42) CV% = 44

[61] - PK Population: Cycle 1 Day 1 (N=4), CV% = 26.8; Cycle 1 Day 14 (N=3) CV% = 97.8

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Area Under the Concentration Versus Time Curve From Time Zero to the Last Quantifiable Concentration (AUClast) for MEN1703

End point title	Part 1 and Part 2: Area Under the Concentration Versus Time Curve From Time Zero to the Last Quantifiable Concentration (AUClast) for MEN1703

End point description:

Nominal blood samples were taken at designated timepoints for evaluation of concentration levels of MEN1703 in plasma. AUClast was calculated by the linear trapezoidal rule. Results are reported in hour times nanograms/millilitre (h*ng/mL). Standard error not reported (0000), arithmetic CV% reported instead. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point at the specified time points.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (pre-dose, up to 24 hours post dose) (21 days/cycle)

End point values	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[62]	3[63]	3[64]	6[65]
Units: h*ng/mL				
arithmetic mean (standard error)	152.17 (± 0000)	490.37 (± 0000)	729.48 (± 0000)	1016.62 (± 0000)

Notes:

[62] - PK Population: CV% = 43

[63] - PK Population: CV% = 24.3

[64] - PK Population: CV% = 116.3

[65] - PK Population: CV% = 69.5

End point values	Cohort 5 (125 mg)	Cohort 6 (150 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[66]	4[67]		
Units: h*ng/mL				
arithmetic mean (standard error)	1936.61 (± 0000)	2608.31 (± 0000)		

Notes:

[66] - PK Population: CV% = 64.2

[67] - PK Population: CV% = 47

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Area Under the Concentration Versus Time Curve From Time Zero to 24 Hours (AUC0-24) for MEN1703

End point title	Part 1 and Part 2: Area Under the Concentration Versus Time Curve From Time Zero to 24 Hours (AUC0-24) for MEN1703[68]

End point description:

Nominal blood samples were taken at designated timepoints for evaluation of concentration levels of MEN1703 in plasma. AUC0-24 was calculated by the linear trapezoidal rule. Results are reported in h*ng/mL. Standard error not reported (0000), arithmetic CV% reported instead. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point at the specified time point.

End point type	Secondary

End point timeframe:

Day 14 of Cycle 1 (pre-dose, up to 120 hours post dose) (21 days/cycle)

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected only for Cohorts 2-6 for this end point.

End point values	Cohort 2 (50 mg)	Cohort 3 (75 mg)	Cohort 4 (100 mg)	Cohort 5 (125 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[69]	3[70]	6[71]	38[72]
Units: h*ng/mL				
arithmetic mean (standard error)	1330.03 (± 0000)	2885.33 (± 0000)	5574.10 (± 0000)	9224.62 (± 0000)

Notes:

[69] - PK Population: CV% = 78.4

[70] - PK Population: CV% = 66.7

[71] - PK Population: CV% = 52.6

[72] - PK Population: CV% = 50.6

End point values	Cohort 6 (150 mg)			
Subject group type	Reporting group			
Number of subjects analysed	3[73]			
Units: h*ng/mL				
arithmetic mean (standard error)	15769.60 (± 0000)			

Notes:

[73] - PK Population: CV% = 106.3

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were assessed up to 21 months. All-cause mortality, survival (RFS, EFS, OS), ORR, PR rate, and DOR were assessed up to 32 months.	
Adverse event reporting additional description:	
All reported safety data based upon the Safety Population: all participants that received at least 1 dose of MEN1703.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Cohort 1 (25 mg)
Reporting group description:	
Participants received MEN1703 (25 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 2 (50 mg)
Reporting group description:	
Participants received MEN1703 (50 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 3 (75 mg)
Reporting group description:	
Participants received MEN1703 (75 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 4 (100 mg)
Reporting group description:	
Participants received MEN1703 (100 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 5 (125 mg)
Reporting group description:	
Participants received MEN1703 (125 mg) orally once daily for 14 consecutive days in cycles of 21 days.	
Reporting group title	Cohort 6 (150 mg)
Reporting group description:	
Participants received MEN1703 (150 mg) orally once daily for 14 consecutive days in cycles of 21 days.	

Serious adverse events	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	3 / 3 (100.00%)
number of deaths (all causes)	2	3	3
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Septic shock			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral venous thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Hyphaema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odynophagia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fasciitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis fungal			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic abscess			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4 (100 mg)	Cohort 5 (125 mg)	Cohort 6 (150 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	35 / 55 (63.64%)	4 / 4 (100.00%)
number of deaths (all causes)	1	35	4
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Asthenia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (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
Immune system disorders			
Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Hypoxia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (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
Asthma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Acute pulmonary oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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

Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (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			
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (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
Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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			
Atrial tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (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
Supraventricular tachycardia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (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	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (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
Nervous system disorders			
Cerebral venous thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Haemorrhage intracranial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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			
Leukocytosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (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
Febrile neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	8 / 55 (14.55%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	2 / 10	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Hyphaema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
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			
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Intestinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Odynophagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Joint effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Fasciitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (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
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (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			
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (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
Anorectal infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (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
Cellulitis			

subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (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
Pneumonia fungal			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	17 / 55 (30.91%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 18	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 6	0 / 0
Laryngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Gastroenteritis clostridial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Sinusitis fungal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Splenic abscess			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (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
Systemic infection			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (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
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	5 / 55 (9.09%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (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
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1 (25 mg)	Cohort 2 (50 mg)	Cohort 3 (75 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pallor			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Orthostatic hypotension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Pain			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Generalised oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Vulval ulceration			
subjects affected / exposed[1]	0 / 1 (0.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dysphonia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Dyspnoea exertional			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhonchi			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tachypnoea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Wheezing			

subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Flat affect			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Agitation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Depressed mood			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Bilirubin conjugated increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Blood bilirubin increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Breath sounds abnormal			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram abnormal			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Prothrombin level increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Troponin I increased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
White blood cell count increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Transfusion reaction			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Overdose			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Face injury			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye injury			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	3
Arthropod sting			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Animal bite			

subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Left ventricular hypertrophy			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pericardial effusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Right ventricular failure			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Cerebral ischaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dizziness			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dysarthria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Carotid artery stenosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hemiparesis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Spinal cord oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Lymphocytosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	3 / 3 (100.00%)
occurrences (all)	0	4	3
Lymphopenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Spontaneous haematoma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pancytopenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	3	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Conjunctival haemorrhage			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Periorbital swelling			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Orbital oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Anorectal discomfort			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Anal ulcer			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal tenderness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	1
Abdominal distension			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0

Diarrhoea			
subjects affected / exposed	1 / 2 (50.00%)	2 / 3 (66.67%)	1 / 3 (33.33%)
occurrences (all)	1	4	1
Oesophagitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mouth haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Faeces soft			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal wall thickening			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tongue discolouration			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Oral mucosal blistering			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cholestasis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Jaundice			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Petechiae			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Skin burning sensation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Purpura			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin mass			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Muscular weakness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint effusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Limb mass			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mobility decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Polyarthritis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Infections and infestations			
Bronchitis viral			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lung infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Herpes virus infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erysipelas			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed[2]	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Systemic mycosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Superinfection fungal			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin candida			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin bacterial infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1

Fluid overload			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypermagnesaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	1	2
Hypertriglyceridaemia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Hypernatraemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Hyponatraemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Hypophosphataemia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	1	2	3
Tumour lysis syndrome			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4 (100 mg)	Cohort 5 (125 mg)	Cohort 6 (150 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	52 / 55 (94.55%)	4 / 4 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pallor			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Orthostatic hypotension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Chills			

subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Face oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	19 / 55 (34.55%)	0 / 4 (0.00%)
occurrences (all)	0	22	0
Fatigue			
subjects affected / exposed	3 / 6 (50.00%)	7 / 55 (12.73%)	3 / 4 (75.00%)
occurrences (all)	5	7	3
Pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Peripheral swelling			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	5 / 55 (9.09%)	1 / 4 (25.00%)
occurrences (all)	0	7	1
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Generalised oedema			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema			

subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	2 / 6 (33.33%)	6 / 55 (10.91%)	2 / 4 (50.00%)
occurrences (all)	2	11	2
Reproductive system and breast disorders			
Vulval ulceration			
subjects affected / exposed[1]	0 / 3 (0.00%)	1 / 24 (4.17%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	2 / 6 (33.33%)	4 / 55 (7.27%)	2 / 4 (50.00%)
occurrences (all)	2	4	2
Dyspnoea exertional			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hiccups			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			

subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhonchi			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Tachypnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Psychiatric disorders			
Flat affect			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Agitation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	2 / 6 (33.33%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Depressed mood			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	4 / 55 (7.27%)	0 / 4 (0.00%)
occurrences (all)	1	5	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	9 / 55 (16.36%)	3 / 4 (75.00%)
occurrences (all)	3	10	4
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	13 / 55 (23.64%)	2 / 4 (50.00%)
occurrences (all)	4	15	3
Bilirubin conjugated increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)	7 / 55 (12.73%)	1 / 4 (25.00%)
occurrences (all)	2	8	1
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	2 / 4 (50.00%)
occurrences (all)	1	2	3
Blood cholesterol increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood triglycerides increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood uric acid increased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Breath sounds abnormal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
C-reactive protein increased			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Electrocardiogram abnormal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	3 / 6 (50.00%)	4 / 55 (7.27%)	1 / 4 (25.00%)
occurrences (all)	8	6	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	4 / 55 (7.27%)	0 / 4 (0.00%)
occurrences (all)	0	4	0
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	2 / 4 (50.00%)
occurrences (all)	0	2	2
Lymphocyte count decreased			
subjects affected / exposed	2 / 6 (33.33%)	4 / 55 (7.27%)	0 / 4 (0.00%)
occurrences (all)	6	14	0
Lymphocyte count increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Fibrin D dimer increased			

subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Platelet count decreased			
subjects affected / exposed	3 / 6 (50.00%)	4 / 55 (7.27%)	0 / 4 (0.00%)
occurrences (all)	5	7	0
Prothrombin level increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Troponin I increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	1 / 4 (25.00%)
occurrences (all)	2	3	1
White blood cell count decreased			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	1	6	0
White blood cell count increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	1 / 4 (25.00%)
occurrences (all)	1	2	2
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Transfusion reaction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Procedural pain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Overdose			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Face injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	1 / 4 (25.00%)
occurrences (all)	1	3	1
Arthropod sting			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Animal bite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Left ventricular hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Right ventricular failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cerebral ischaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	2 / 4 (50.00%)
occurrences (all)	0	2	2
Dizziness postural			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dysarthria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Carotid artery stenosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	3 / 6 (50.00%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	3	3	0
Hemiparesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypoaesthesia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Spinal cord oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Leukocytosis			
subjects affected / exposed	0 / 6 (0.00%)	7 / 55 (12.73%)	0 / 4 (0.00%)
occurrences (all)	0	8	0
Lymphocytosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Anaemia			
subjects affected / exposed	3 / 6 (50.00%)	17 / 55 (30.91%)	0 / 4 (0.00%)
occurrences (all)	3	18	0
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	6 / 55 (10.91%)	1 / 4 (25.00%)
occurrences (all)	0	6	1

Spontaneous haematoma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pancytopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	13 / 55 (23.64%)	1 / 4 (25.00%)
occurrences (all)	0	14	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Periorbital swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Orbital oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Anorectal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Anal ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Abdominal tenderness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			

subjects affected / exposed	0 / 6 (0.00%)	6 / 55 (10.91%)	0 / 4 (0.00%)
occurrences (all)	0	7	0
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	6 / 55 (10.91%)	1 / 4 (25.00%)
occurrences (all)	2	6	1
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	9 / 55 (16.36%)	1 / 4 (25.00%)
occurrences (all)	1	9	1
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)	4 / 55 (7.27%)	0 / 4 (0.00%)
occurrences (all)	1	4	0
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)	7 / 55 (12.73%)	2 / 4 (50.00%)
occurrences (all)	2	11	2
Oesophagitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	26 / 55 (47.27%)	2 / 4 (50.00%)
occurrences (all)	2	31	2
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Mouth haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Faeces soft			

subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Glossodynia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gingival pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gingival bleeding			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Gastrointestinal wall thickening			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	13 / 55 (23.64%)	1 / 4 (25.00%)
occurrences (all)	1	13	1
Tongue discolouration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	4 / 55 (7.27%)	0 / 4 (0.00%)
occurrences (all)	0	4	0
Rectal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Proctalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Paraesthesia oral			

subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oral mucosal blistering			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cholestasis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Jaundice			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dermatitis acneiform			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eczema			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin burning sensation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Purpura			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	5	0
Skin mass			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	3	0

Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Muscular weakness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Joint effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Limb mass			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Mobility decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Bone pain			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	2 / 6 (33.33%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	2	4	0
Polyarthritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Spinal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Gingivitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Herpes virus infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Erysipelas			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Vulvovaginal mycotic infection			
subjects affected / exposed[2]	0 / 3 (0.00%)	0 / 24 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Systemic mycosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Superinfection fungal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin candida			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Skin bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	1 / 6 (16.67%)	9 / 55 (16.36%)	2 / 4 (50.00%)
occurrences (all)	1	9	2
Fluid overload			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	2 / 6 (33.33%)	6 / 55 (10.91%)	0 / 4 (0.00%)
occurrences (all)	3	11	0
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Hypermagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	8 / 55 (14.55%)	1 / 4 (25.00%)
occurrences (all)	2	8	1
Hypertriglyceridaemia			

subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Hyperuricaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	1 / 4 (25.00%)
occurrences (all)	2	4	1
Hypocalcaemia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	0 / 4 (0.00%)
occurrences (all)	1	6	0
Hypernatraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	2 / 6 (33.33%)	7 / 55 (12.73%)	1 / 4 (25.00%)
occurrences (all)	4	10	1
Hypophosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	6 / 55 (10.91%)	0 / 4 (0.00%)
occurrences (all)	0	6	0
Tumour lysis syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event affected only female participants.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This adverse event affected only female participants.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2017	- Adjusted threshold for leukocyte count prior to first dose (previously defined as ≥ 50x10^9/litre [L], now defined as greater than 30x10^9/L) and extended use of hydroxyurea during Cycle 1 - Revision to exceptions to serious adverse event reporting (SAE) reporting
21 November 2017	- Revision of Dose-finding Schema to a Standard 3 + 3 Design - Update to Risk Information - Revision of the Study Evaluations to include a comprehensive evaluation of Coagulation Abnormalities in participants who develop such abnormalities during study treatment
06 December 2017	- Revision of Dose-finding Schema to a Standard 3 + 3 Design - Update to Risk Information - Revision of the Study Evaluations to include a comprehensive evaluation of Coagulation Abnormalities in participants who develop such abnormalities during study treatment - Revision to DLT Criterion for Electrolyte Imbalances and the Addition of Guidance for the Management of Hypophosphatemia - Revised Dosing Instructions for MEN1703 - Additional PK Sampling and cytochrome P450 2D6 Phenotyping - Modification to the Electrocardiogram Monitoring Plan
26 April 2018	- Introduction of Formulated MEN1703 - Removal of bleeding time from coagulation assessment - Additional Pharmacodynamic (PD) Sampling and modifications of PD samples processing - Changes to samplings for genetic profiling - Use of leftover PK samples for metabolite identification analysis
25 February 2019	- The restoring of dose escalation beyond 125 mg and up to 400 mg in Part 1 - The amended DLT definition and list - The change of study Part 2 design - The introduction of FMS-like tyrosine kinase 3 (FLT3) mutation status and CD25 expression at baseline which could be used for potential retrospective and post-hoc exploratory analyses in both study Parts - The new schedule of assessment for bone marrow aspirate / biopsy - The inclusion of minimal residual disease (MRD) assessment - Additional PD/PK sampling and removal of PD assessment in bone marrow - The inclusion of AML karyotypic analysis
21 May 2019	- Change in design of Part 1: up to 4 additional participants will be treated at 150 mg formulated investigative medicinal product according to a Bayesian modified toxicity probability interval with a target toxicity rate ≤ 25%. Should none of these 4 participants experience a DLT, higher dose levels may be considered and will be subject to a protocol amendment
05 August 2019	- The further investigation of the 150 mg dose level - The amended DLT definition and list - The change of study Part 2 design - The introduction of FLT3 mutation status and CD25 expression as retrospective exploratory analyses in both study Parts - The new schedule of assessment for bone marrow aspirate/biopsy - The inclusion of MRD assessment - Additional PD/PK sampling and removal of PD assessment in bone marrow - The inclusion of AML karyotypic analysis - The introduction of antibiotics and antifungals prophylaxis

21 February 2020	- Expansion of the 125 mg (maximum tolerated dose/recommended dose) Cohort in additional 20 participants - Addition of CRh as additional anti-leukemic activity read-out - Removal of the statement requiring study hold in case of fatal related events - Introduction of additional of PD time-points
24 March 2020	- Change in PD biomarkers sampling
10 June 2020	- Notification that photosensitivity / phototoxicity effect cannot be excluded - Appointment of a centralized Study Drug Safety Unit team to the study which will be responsible for the management of AEs from all the sites in compliance with the applicable regulatory requirements (including SAEs and suspected unexpected serious adverse reaction [SUSARs] management) and all safety communications submitted to the sites, Ras and Ecs accordingly to the procedures described in the corresponding study safety management plan - Other clarifications on reporting of SUSARs and SAEs
01 July 2020	- Inclusion of photosensitivity / phototoxicity preventive measures
20 April 2021	- Inclusion of an additional expansion Cohort of isocitrate dehydrogenase (IDH) mutated participants (IDH mutants) - Adjustment of study assessments windows - Inclusion of the transfusion conversion and maintenance rate as secondary study objectives - Inclusion of allogeneic HSCT rate as secondary study objectives - Reduction of PD sampling timepoints IDH mutants expansion Cohort - Clarification of participant replacement criteria - Clarification of Completion of the Study section and End of Study Definition - Adverse Events and Reporting Requirements section general review and update
27 June 2022	- Modification of the End of Study definition for the participants benefiting of the treatment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported