Clinical trial results:
A randomized, double-blind phase 3 study of vadastuximab talirine (SGN-CD33A) versus placebo in combination with azacitidine or decitabine in the treatment of older patients with newly diagnosed acute myeloid leukemia (AML)

Summary

EudraCT number	2015-003482-28
Trial protocol	CZ HU GB DE BE AT ES NL IT
Global end of trial date	03 October 2017

Results information

Result version number	v1 (current)
This version publication date	18 October 2018
First version publication date	18 October 2018

Trial information

Trial identification

Sponsor protocol code	SGN33A-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02785900
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seattle Genetics, Inc.
Sponsor organisation address	21823 30th Dr SE, Bothell, United States, 98021
Public contact	Chief Medical Officer, Seattle Genetics, Inc., 1 8554732436, medinfo@seagen.com
Scientific contact	Chief Medical Officer, Seattle Genetics, Inc., 1 8554732436, medinfo@seagen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2017
Global end of trial reached?	Yes
Global end of trial date	03 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study in AML patients is to test whether vadastuximab talirine (SGN-CD33A; 33A) combined with either azacitidine or decitabine improves remission rates and extends overall survival as compared to placebo combined with either azacitidine or decitabine.

Protection of trial subjects:

The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with principles enunciated in the declaration, the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP), and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 CFR Parts 11, 50, 54, 56, and 312. The consent form approved by each IRB/IEC included all elements required by the applicable regional laws and regulations, including a statement that Seattle Genetics, Inc. and authorities had access to patient records. Consent was obtained from all patients before any protocol-required procedures were performed, including any procedure not part of normal patient care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 94
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Australia: 21

Worldwide total number of subjects	240
EEA total number of subjects	90

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)	6
From 65 to 84 years	221
85 years and over	13

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The population to be studied includes patients with newly diagnosed, previously untreated, cytologically/histologically confirmed de novo or secondary acute myeloid leukemia, with intermediate or adverse cytogenetic risk per revised UK Medical Research Council classification, who are not considered candidates for alallogeneic stem cell transplant.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	33A + HMA

Arm description:

33A plus azacitidine or decitabine

Arm type	Experimental
Investigational medicinal product name	Vadatuximab talirine
Investigational medicinal product code	
Other name	SGN-CD33A
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mcg/kg every 4 weeks via intravenous (IV) push

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

75 mg/m2 given subcutaneously (SC) or IV x 7 days, every 4 weeks

Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/m2 given IV x 5 days, every 4 weeks

Arm title	Placebo + HMA

Arm description:

placebo plus azacitidine or decitabine

Arm type	Active comparator

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

75 mg/m2 given subcutaneously (SC) or IV x 7 days, every 4 weeks

Investigational medicinal product name	Decitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/m2 given IV x 5 days, every 4 weeks

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Volume equivalent to 10 mcg/kg, every 4 weeks via IV push

Number of subjects in period 1	33A + HMA	Placebo + HMA
Started	117	123
Completed	0	0
Not completed	117	123
Adverse event, serious fatal	46	32
Consent withdrawn by subject	4	8
Physician decision	3	2
Study Termination by Sponsor	64	81

Baseline characteristics

Reporting groups	
Reporting group title	33A + HMA
Reporting group description: 33A plus azacitidine or decitabine	
Reporting group title	Placebo + HMA
Reporting group description: placebo plus azacitidine or decitabine	

Reporting group values	33A + HMA	Placebo + HMA	Total
Number of subjects	117	123	240
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	6
From 65-84 years	109	112	221
85 years and over	5	8	13
Age continuous Units: years			
median	75.0	75.0	
full range (min-max)	62 to 91	52 to 91	-
Gender categorical Units: Subjects			
Female	69	67	136
Male	48	56	104
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	2	5
Not Hispanic or Latino	98	111	209
Unknown or Not Reported	16	10	26
Race/Ethnicity Units: Subjects			
Asian	12	16	28
Black or African American	3	1	4
White	85	94	179
Other	2	1	3
Not Reportable	13	10	23
Unknown	2	1	3
Eastern Cooperative Oncology Group (ECOG) Performance Status			
0=Normal activity; 1=Symptoms but ambulatory; 2=In bed less than 50% of the time; 3= In bed more than 50% of the time; 4=100% bedridden; 5=Dead			
Units: Subjects			
Grade 0: Normal activity	23	23	46
Grade 1: Symptoms but ambulatory	78	80	158
Grade 2: In bed less than 50% of the time	16	20	36

End points

End points reporting groups

Reporting group title	33A + HMA
Reporting group description: 33A plus azacitidine or decitabine	
Reporting group title	Placebo + HMA
Reporting group description: placebo plus azacitidine or decitabine	
Subject analysis set title	33A + HMA (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Defined as randomized patients: 117 patients randomized to the experimental arm and 123 patients randomized to the comparator arm.	
Subject analysis set title	33A + HMA (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set includes all patients who received any dose of blinded study treatment (vadatuximab talirine or placebo) or HMA. The safety analysis set for the experimental arm consisted of 111 patients who received at least 1 dose of vadatuximab talirine (110 patients randomized to the experimental arm, and 1 patient randomized to the comparator arm who received vadatuximab talirine in error during Cycle 1). The safety analysis set for the comparator arm consisted of 128 patients (114 patients who received both HMA and placebo, 7 patients randomized to the comparator arm who received HMA only, and 7 patients randomized to the experimental arm who received HMA only).	
Subject analysis set title	Placebo +HMA (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Defined as randomized patients: 117 patients randomized to the experimental arm and 123 patients randomized to the comparator arm.	
Subject analysis set title	Placebo + HMA (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set includes all patients who received any dose of blinded study treatment (vadatuximab talirine or placebo) or HMA. The safety analysis set for the experimental arm consisted of 111 patients who received at least 1 dose of vadatuximab talirine (110 patients randomized to the experimental arm, and 1 patient randomized to the comparator arm who received vadatuximab talirine in error during Cycle 1). The safety analysis set for the comparator arm consisted of 128 patients (114 patients who received both HMA and placebo, 7 patients randomized to the comparator arm who received HMA only, and 7 patients randomized to the experimental arm who received HMA only).	

Primary: Overall Survival

End point title	Overall Survival[1]
End point description:	
End point type	Primary
End point timeframe: Up to 1.5 years	

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: Descriptive statistics have been reported for this outcome.

End point values	33A + HMA	Placebo + HMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	123		
Units: months				
median (full range (min-max))	5.1 (0.30 to 11.99)	999 (0.13 to 999)		

Statistical analyses

No statistical analyses for this end point

Primary: Composite Complete Remission Rate

End point title	Composite Complete Remission Rate[2]

End point description:

Number of patients who acheived CR or CRi

End point type	Primary

End point timeframe:

Up to 1.5 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics have been reported for this outcome.

End point values	33A + HMA	Placebo + HMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	123		
Units: participants				
number (confidence interval 95%)	30 (18 to 34.5)	26 (14.3 to 29.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Remission

End point title	Duration of Remission

End point description:

Duration of remission is calculated from the first documentation of CR or CRi to the first documentation of disease relapse or death, whichever comes first. Patients who are in remission at the time of analysis cutoff are censored at the date of last response assessment. Patients who started another anticancer therapy before relapse or death are censored at the date of last reponse assessment prior to start of new therapy.

End point type	Secondary

End point timeframe:

Up to approximately 9.5 months

End point values	33A + HMA	Placebo + HMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	26		
Units: months				
median (full range (min-max))	5.1 (0.03 to 6.21)	7.5 (0.03 to 9.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival

End point title	Event-free Survival

End point description:

Event-free survival is calculated from the time of randomization to the first documentation of progression, relapse, or death, whichever comes first. Patients who do not have event (progression, relapse, or death) prior to analysis cutoff date are consored at the date of last response assessment. Patients who started another anticancer therapy before progression, relapse, or death are censored at the date of last response assessment prior to the start of new therapy. Patients who do not have response assessment post-baseline are censored at the date of randomization.

End point type	Secondary

End point timeframe:

Up to approximately 11.24 months

End point values	33A + HMA	Placebo + HMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	123		
Units: months				
median (confidence interval 95%)	4.2 (3.5 to 5.1)	6.7 (4.5 to 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Leukemia-free Survival

End point title	Leukemia-free Survival

End point description:

Leukemia-free survival is calculated from the first documentation of blast clearance (CR, CRi, mLFS) to the first documentation of disease relapse or death, whichever comes first. Patients who are in remission at the time of analysis cutoff are censored at the date of last response assessment. Patients who started another anticancer therapy before relapse or death are censored at the date of last response assessment prior to start of new therapy.

End point type	Secondary

End point timeframe:

Up to approximately 9.49 months

End point values	33A + HMA	Placebo + HMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	26		
Units: months				
median (full range (min-max))	5.1 (0.03 to 8.31)	7.5 (0.03 to 9.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Type, Incidence, Severity, Seriousness, and Relatedness of Adverse Events

End point title	Type, Incidence, Severity, Seriousness, and Relatedness of Adverse Events

End point description:

Treatment-emergent adverse events (TEAEs) are presented and defined as newly occurring (not present at baseline) or worsening after first dose of investigational product. SAE = serious adverse event. "Study treatment" in this data set refers to blinded study treatment.

End point type	Secondary

End point timeframe:

Up to 1.5 years

End point values	33A + HMA (Safety)	Placebo + HMA (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	128		
Units: participants				
Patient with any TEAE	111	125		
Patients with any AE related to study treatment	83	59		
Patients with any SAE	92	89		
Patients with any SAE related to study treatment	51	20		
Patients with Grade 3 or Higher AE	103	112		

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory Abnormalities

End point title	Laboratory Abnormalities
End point description:	
Participants who experienced a laboratory grade increase to Grade 3 or higher	
End point type	Secondary
End point timeframe:	
Up to approximately 1 year	

End point values	33A + HMA (Safety)	Placebo + HMA (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	128		
Units: participants				
Alanine Aminotransferase (IU/L) - High	0	2		
Albumin (g/dL) - Low	2	4		
Alkaline Phosphatase (IU/L) - High	0	2		
Amylase (IU/L) - High	1	0		
Aspartate Aminotransferase (IU/L) - High	1	2		
Bilirubin (mg/dL) - High	1	1		
Calcium (mg/dL) - Low	8	3		
Creatinine (mg/dL) - High	0	1		
Glucose (mg/dL) - High	12	9		
Magnesium (mg/dL) - High	2	0		
Phosphate (mg/dL) - Low	17	9		
Potassium (mEq/L) - High	1	0		
Potassium (mEq/L) - Low	5	14		
Sodium (mEq/L) - Low	13	12		
Triacylglycerol Lipase (IU/L) - High	10	4		
Urate (mg/dL) - High	4	7		
Hemoglobin (g/dL) - Low	59	66		
Leukocytes (x10^3/uL) - High	0	3		
Leukocytes (x10^3/uL) - Low	86	70		
Lymphocytes (x10^3/uL) - High	1	4		
Lymphocytes (x10^3/uL) - Low	51	29		
Neutrophils (x10^3/uL) - Low	63	43		
Platelets (x10^3/uL) - Low	77	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Remission

End point title	Time to Complete Remission

End point description:

Time to CR or CRi is the time from randomization to the first documentation of CR/CRi

End point type	Secondary

End point timeframe:

Up to 26 months

End point values	33A + HMA	Placebo + HMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	26		
Units: weeks				
median (full range (min-max))	9.3 (5 to 22)	9.4 (7 to 26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality Rates at Day 30 and Day 60

End point title	Mortality Rates at Day 30 and Day 60

End point description:

End point type	Secondary

End point timeframe:

Up to 60 days

End point values	33A + HMA	Placebo + HMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	123		
Units: percentage of participants				
number (confidence interval 95%)				
30-day Mortality Rate	11 (7 to 18)	6 (3 to 12)		
60-day Mortality Rate	23 (16 to 32)	13 (8 to 20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease (MRD)-Negative Composite Complete Remission Rate

End point title	Minimal Residual Disease (MRD)-Negative Composite Complete Remission Rate

End point description:

End point type	Secondary

End point timeframe:

Up to 1.5 years

End point values	33A + HMA	Placebo + HMA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	123		
Units: participants				
number (confidence interval 95%)				
MRD-negative CRc rate	18 (9.4 to 23.2)	10 (4 to 14.4)		
MRD-negative CR rate	8 (3 to 13)	5 (1.3 to 9.2)		
MRD-negative CRi rate	10 (4.2 to 15.2)	5 (1.3 to 9.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 13 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	33A + HMA
Reporting group description: 33A plus azacitidine or decitabine	
Reporting group title	Placebo + HMA
Reporting group description: -	

Serious adverse events	33A + HMA	Placebo + HMA	
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 111 (82.88%)	89 / 128 (69.53%)	
number of deaths (all causes)	43	34	
number of deaths resulting from adverse events	34	28	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 111 (0.90%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Malignant melanoma			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic renal cell carcinoma			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 111 (0.90%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 111 (1.80%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 111 (7.21%)	8 / 128 (6.25%)	
occurrences causally related to treatment / all	3 / 8	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 111 (0.90%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Fatigue			
subjects affected / exposed	0 / 111 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 111 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Oedema peripheral			
subjects affected / exposed	2 / 111 (1.80%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Social circumstances			
Blood product transfusion dependent			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 111 (2.70%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Epistaxis			
subjects affected / exposed	3 / 111 (2.70%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 111 (0.90%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

Pulmonary oedema			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Confusional state			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood culture positive			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatinine increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	2 / 111 (1.80%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fall			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transfusion reaction			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 111 (1.80%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 111 (1.80%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 111 (0.90%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serotonin syndrome			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	39 / 111 (35.14%)	31 / 128 (24.22%)	
occurrences causally related to treatment / all	32 / 55	11 / 39	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	6 / 111 (5.41%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	5 / 7	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	5 / 111 (4.50%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	3 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	5 / 111 (4.50%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	3 / 111 (2.70%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	2 / 111 (1.80%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	2 / 111 (1.80%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 111 (2.70%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	2 / 111 (1.80%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal haemorrhage			
subjects affected / exposed	2 / 111 (1.80%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 111 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhoids			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palatal oedema			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis cholestatic			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Vasculitic rash			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 111 (0.90%)	4 / 128 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract pain			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Pneumonia			
subjects affected / exposed	22 / 111 (19.82%)	15 / 128 (11.72%)	
occurrences causally related to treatment / all	7 / 24	5 / 16	
deaths causally related to treatment / all	2 / 4	1 / 3	
Sepsis			
subjects affected / exposed	14 / 111 (12.61%)	7 / 128 (5.47%)	
occurrences causally related to treatment / all	5 / 15	1 / 10	
deaths causally related to treatment / all	4 / 8	0 / 3	
Cellulitis			
subjects affected / exposed	6 / 111 (5.41%)	8 / 128 (6.25%)	
occurrences causally related to treatment / all	3 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	9 / 111 (8.11%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	3 / 10	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock			
subjects affected / exposed	6 / 111 (5.41%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 111 (1.80%)	4 / 128 (3.13%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 111 (1.80%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 111 (0.90%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	2 / 111 (1.80%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	3 / 111 (2.70%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 111 (1.80%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related infection			
subjects affected / exposed	2 / 111 (1.80%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 111 (1.80%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	2 / 111 (1.80%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	2 / 111 (1.80%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Catheter site cellulitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Parotitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subcutaneous abscess			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 111 (0.90%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 111 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dehydration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			

subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 111 (0.90%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	33A + HMA	Placebo + HMA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 111 (94.59%)	123 / 128 (96.09%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	12 / 111 (10.81%)	9 / 128 (7.03%)	
occurrences (all)	12	11	
Haematoma			
subjects affected / exposed	9 / 111 (8.11%)	9 / 128 (7.03%)	
occurrences (all)	11	12	
Hypertension			

subjects affected / exposed	7 / 111 (6.31%)	3 / 128 (2.34%)	
occurrences (all)	7	3	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	33 / 111 (29.73%)	23 / 128 (17.97%)	
occurrences (all)	38	28	
Fatigue			
subjects affected / exposed	25 / 111 (22.52%)	24 / 128 (18.75%)	
occurrences (all)	27	25	
Pyrexia			
subjects affected / exposed	25 / 111 (22.52%)	18 / 128 (14.06%)	
occurrences (all)	38	31	
Asthenia			
subjects affected / exposed	13 / 111 (11.71%)	14 / 128 (10.94%)	
occurrences (all)	16	14	
Injection site erythema			
subjects affected / exposed	11 / 111 (9.91%)	4 / 128 (3.13%)	
occurrences (all)	18	6	
Chills			
subjects affected / exposed	8 / 111 (7.21%)	4 / 128 (3.13%)	
occurrences (all)	9	5	
Localised oedema			
subjects affected / exposed	6 / 111 (5.41%)	0 / 128 (0.00%)	
occurrences (all)	11	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	17 / 111 (15.32%)	28 / 128 (21.88%)	
occurrences (all)	20	31	
Cough			
subjects affected / exposed	20 / 111 (18.02%)	20 / 128 (15.63%)	
occurrences (all)	22	25	
Epistaxis			
subjects affected / exposed	21 / 111 (18.92%)	11 / 128 (8.59%)	
occurrences (all)	32	12	
Pleural effusion			

subjects affected / exposed	12 / 111 (10.81%)	5 / 128 (3.91%)	
occurrences (all)	15	5	
Oropharyngeal pain			
subjects affected / exposed	6 / 111 (5.41%)	6 / 128 (4.69%)	
occurrences (all)	7	6	
Hypoxia			
subjects affected / exposed	6 / 111 (5.41%)	4 / 128 (3.13%)	
occurrences (all)	6	5	
Pulmonary oedema			
subjects affected / exposed	7 / 111 (6.31%)	3 / 128 (2.34%)	
occurrences (all)	7	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	21 / 111 (18.92%)	12 / 128 (9.38%)	
occurrences (all)	22	13	
Confusional state			
subjects affected / exposed	7 / 111 (6.31%)	7 / 128 (5.47%)	
occurrences (all)	9	7	
Anxiety			
subjects affected / exposed	8 / 111 (7.21%)	4 / 128 (3.13%)	
occurrences (all)	8	4	
Investigations			
Weight decreased			
subjects affected / exposed	15 / 111 (13.51%)	17 / 128 (13.28%)	
occurrences (all)	17	17	
Platelet count decreased			
subjects affected / exposed	12 / 111 (10.81%)	10 / 128 (7.81%)	
occurrences (all)	19	12	
Blood creatinine increased			
subjects affected / exposed	9 / 111 (8.11%)	7 / 128 (5.47%)	
occurrences (all)	10	9	
Neutrophil count decreased			
subjects affected / exposed	6 / 111 (5.41%)	8 / 128 (6.25%)	
occurrences (all)	8	13	
White blood cell count decreased			

subjects affected / exposed	6 / 111 (5.41%)	5 / 128 (3.91%)	
occurrences (all)	8	10	
Blood bilirubin increased			
subjects affected / exposed	6 / 111 (5.41%)	1 / 128 (0.78%)	
occurrences (all)	6	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	11 / 111 (9.91%)	7 / 128 (5.47%)	
occurrences (all)	14	11	
Fall			
subjects affected / exposed	10 / 111 (9.01%)	5 / 128 (3.91%)	
occurrences (all)	13	5	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 111 (7.21%)	3 / 128 (2.34%)	
occurrences (all)	8	3	
Sinus tachycardia			
subjects affected / exposed	7 / 111 (6.31%)	3 / 128 (2.34%)	
occurrences (all)	7	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 111 (5.41%)	17 / 128 (13.28%)	
occurrences (all)	6	18	
Headache			
subjects affected / exposed	5 / 111 (4.50%)	17 / 128 (13.28%)	
occurrences (all)	7	18	
Dysgeusia			
subjects affected / exposed	7 / 111 (6.31%)	5 / 128 (3.91%)	
occurrences (all)	7	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	49 / 111 (44.14%)	59 / 128 (46.09%)	
occurrences (all)	78	105	
Thrombocytopenia			
subjects affected / exposed	39 / 111 (35.14%)	47 / 128 (36.72%)	
occurrences (all)	73	67	

Neutropenia			
subjects affected / exposed	19 / 111 (17.12%)	24 / 128 (18.75%)	
occurrences (all)	35	34	
Febrile neutropenia			
subjects affected / exposed	25 / 111 (22.52%)	12 / 128 (9.38%)	
occurrences (all)	29	18	
Leukopenia			
subjects affected / exposed	13 / 111 (11.71%)	8 / 128 (6.25%)	
occurrences (all)	23	9	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	6 / 111 (5.41%)	2 / 128 (1.56%)	
occurrences (all)	8	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	39 / 111 (35.14%)	54 / 128 (42.19%)	
occurrences (all)	48	64	
Nausea			
subjects affected / exposed	37 / 111 (33.33%)	45 / 128 (35.16%)	
occurrences (all)	49	56	
Diarrhoea			
subjects affected / exposed	34 / 111 (30.63%)	34 / 128 (26.56%)	
occurrences (all)	47	52	
Vomiting			
subjects affected / exposed	15 / 111 (13.51%)	31 / 128 (24.22%)	
occurrences (all)	25	41	
Abdominal pain			
subjects affected / exposed	11 / 111 (9.91%)	12 / 128 (9.38%)	
occurrences (all)	13	15	
Mouth ulceration			
subjects affected / exposed	7 / 111 (6.31%)	9 / 128 (7.03%)	
occurrences (all)	7	9	
Stomatitis			
subjects affected / exposed	8 / 111 (7.21%)	6 / 128 (4.69%)	
occurrences (all)	10	7	
Dyspepsia			

subjects affected / exposed	10 / 111 (9.01%)	1 / 128 (0.78%)	
occurrences (all)	10	1	
Haemorrhoids			
subjects affected / exposed	4 / 111 (3.60%)	7 / 128 (5.47%)	
occurrences (all)	5	7	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	11 / 111 (9.91%)	15 / 128 (11.72%)	
occurrences (all)	15	19	
Pruritus			
subjects affected / exposed	7 / 111 (6.31%)	13 / 128 (10.16%)	
occurrences (all)	8	13	
Erythema			
subjects affected / exposed	3 / 111 (2.70%)	8 / 128 (6.25%)	
occurrences (all)	4	10	
Purpura			
subjects affected / exposed	6 / 111 (5.41%)	2 / 128 (1.56%)	
occurrences (all)	6	2	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 111 (5.41%)	6 / 128 (4.69%)	
occurrences (all)	6	8	
Urinary retention			
subjects affected / exposed	6 / 111 (5.41%)	2 / 128 (1.56%)	
occurrences (all)	6	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 111 (9.01%)	10 / 128 (7.81%)	
occurrences (all)	10	12	
Back pain			
subjects affected / exposed	5 / 111 (4.50%)	9 / 128 (7.03%)	
occurrences (all)	5	10	
Pain in extremity			
subjects affected / exposed	7 / 111 (6.31%)	6 / 128 (4.69%)	
occurrences (all)	12	6	
Muscular weakness			

subjects affected / exposed	6 / 111 (5.41%)	3 / 128 (2.34%)	
occurrences (all)	6	3	
Infections and infestations			
Cellulitis			
subjects affected / exposed	10 / 111 (9.01%)	10 / 128 (7.81%)	
occurrences (all)	11	10	
Oral candidiasis			
subjects affected / exposed	6 / 111 (5.41%)	9 / 128 (7.03%)	
occurrences (all)	7	10	
Pneumonia			
subjects affected / exposed	10 / 111 (9.01%)	3 / 128 (2.34%)	
occurrences (all)	11	3	
Oral herpes			
subjects affected / exposed	2 / 111 (1.80%)	10 / 128 (7.81%)	
occurrences (all)	2	12	
Urinary tract infection			
subjects affected / exposed	4 / 111 (3.60%)	8 / 128 (6.25%)	
occurrences (all)	4	9	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	28 / 111 (25.23%)	30 / 128 (23.44%)	
occurrences (all)	43	36	
Decreased appetite			
subjects affected / exposed	29 / 111 (26.13%)	28 / 128 (21.88%)	
occurrences (all)	36	29	
Hypomagnesaemia			
subjects affected / exposed	11 / 111 (9.91%)	13 / 128 (10.16%)	
occurrences (all)	17	16	
Hyponatraemia			
subjects affected / exposed	10 / 111 (9.01%)	13 / 128 (10.16%)	
occurrences (all)	12	22	
Hypoalbuminaemia			
subjects affected / exposed	9 / 111 (8.11%)	10 / 128 (7.81%)	
occurrences (all)	10	10	
Hypocalcaemia			

subjects affected / exposed	10 / 111 (9.01%)	8 / 128 (6.25%)	
occurrences (all)	11	8	
Hypophosphataemia			
subjects affected / exposed	8 / 111 (7.21%)	9 / 128 (7.03%)	
occurrences (all)	10	9	
Fluid overload			
subjects affected / exposed	3 / 111 (2.70%)	7 / 128 (5.47%)	
occurrences (all)	3	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2016	- Duration of remission has been added as a secondary objective/endpoint of the study. - Exclusion criteria added: Patients who are medically fit and willing to receive standard intensive induction chemotherapy. - Exclusion criteria added: Any other condition which, in the opinion of the investigator, would compromise patient safety or interfere with data interpretation. - RBC count and MCV have been added to the list of clinical laboratory tests - Definition of the end of the trial added.
20 May 2016	- Lower age limit for study eligibility changed from =>65 to =>18 years. - The eligibility criteria have been revised to require females of childbearing potential to have a negative pregnancy test prior to enrollment as well as to use 2 effective contraceptive methods during the study. Female patients who are breastfeeding have also been excluded from enrollment. - Language edited to better emphasize the recommendations for prophylaxis of neutropenia for patients on the study. - Added: requirement of pregnancy testing at screening and end of treatment for females of childbearing potential. - Added: The modified intent-to-treat (mITT) analysis set will include all patients from the ITT analysis set who receive any dose of blinded study treatment (vadastuximab talirine or placebo) or HMA. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received. - Added: All efficacy endpoints will be analyzed using the ITT analysis set. Supplemental analyses will be performed using the mITT analysis set. - Language added to specify a blinded interim safety analysis to detect differences in early mortality between the arms.

27 March 2017	- Composite complete remission rate (CRc) has been changed from a secondary endpoint to an independent primary endpoint of the trial. The endpoints/objectives have also been re-ordered and revised to clarify that the MRD negative CRc rate will be compared between the treatment arms. - Study stopping criteria added for events of sinusoidal obstructive syndrome/veno-occlusive disease (SOS/VOD). - Inclusion criteria revised to clarify contraceptive requirements for male and female patients as well as clarify restrictions on breastfeeding, pregnancy, and sperm/ova donation. - Inclusion criteria revised to specify that patients 80 years and older must have an ECOG performance status of 0 or 1. - Inclusion criteria revised to clarify contraceptive requirements for male and female patients as well as clarify restrictions on breastfeeding, pregnancy, and sperm/ova donation. - Exclusion criteria added: Patients with supplemental oxygen requirement or resting oxygen saturation of <90%. - Exclusion criteria added: History of clinically significant chronic liver disease (e.g. liver cirrhosis) and/or ongoing alcohol abuse. - Dose modification section revised to ensure patient safety. - Prohibited concomitant medications revised to clarify that allogenic stem cell transplantation is prohibited during treatment period and within 30 days of last dose of blinded study treatment. - Addition of pregnancy test on Day 1 of each cycle of study treatment to ensure patient safety per EU CTFG "Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials." - Pulse oximetry test added at baseline to assess oxygen saturation level at room air. - Measurement of vital signs has been added pre- and within 30 minutes post-blinded study treatment administration. -Follow-up assessments section revised for clarity and to provide information regarding follow-up of adverse events of special interest.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported