



Clinical trial results:

A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Previously Treated Acute Myeloid Leukemia

Summary

EudraCT number	2015-005256-97
Trial protocol	DE BE HU ES GB FR PL SE DK IT
Global end of trial date	01 June 2020

Results information

Result version number	v1
This version publication date	13 June 2021
First version publication date	13 June 2021

Trial information

Trial identification

Sponsor protocol code	SGI-110-06
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02920008
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astex Pharmaceuticals, Inc.
Sponsor organisation address	4420 Rosewood Dr., Pleasanton, United States, 94588
Public contact	Clinical trial info. ASTRAL-2, Astex Pharmaceuticals, Inc., ASTRAL-2@astx.com
Scientific contact	Clinical trial info. ASTRAL-2, Astex Pharmaceuticals, Inc., ASTRAL-2@astx.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	01 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2020
Global end of trial reached?	Yes
Global end of trial date	01 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess and compare overall survival (OS) between guadecitabine and treatment choice (TC) in adults with previously treated acute myeloid leukemia (AML).

TC options are:

- High intensity (intermediate or high dose cytarabine [HiDAC]; mitoxantrone, etoposide, and cytarabine [MEC]; or fludarabine, cytarabine, granulocyte colony stimulating factor [G-CSF], +/- idarubicin [FLAG/FLAG-Ida])
- Low intensity (low dose cytarabine [LDAC], decitabine, or azacitidine)
- Best Supportive Care (BSC)

BSC will be provided to all subjects as per standard and institutional practice.

Protection of trial subjects:

The study was conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Japan: 36
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	United States: 57

Country: Number of subjects enrolled	Ukraine: 4
Worldwide total number of subjects	302
EEA total number of subjects	149

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)	164
From 65 to 84 years	138
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 404 subjects from approximately 100 study centers were to be randomly assigned to either guadacitabine or treatment choice (TC) in a 1:1 ratio (approximately 202 subjects per group). Enrollment was stopped with approximately 300 subjects randomly assigned to treatment based on data monitoring committee recommendation.

Pre-assignment

Screening details:

A total of 358 subjects were assessed for study inclusion. Of these 56 failed screening assessments. A total of 302 subjects were randomized (148 guadecitabine, 154 TC). Of the randomized subjects, 10 did not receive study drug (3 guadecitabine, 7 TC).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Guadacitabine

Arm description:

Guadacitabine was administered subcutaneously (SC) at a dose of 60 mg/m² in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Guadecitabine
Investigational medicinal product code	
Other name	SGI-110
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

60 mg/m² subcutaneously (SC) daily on Days 1-5 and Days 8-12 or on Days 1-10 of the first 28-day cycle. Second cycle could have been 60 mg/m² for either 10 days (Days 1-5 and 8-12 or Days 1-10) or 5 days (Days 1-5 only) based on assessment of disease response, and hematological recovery by Day \geq 28. For Cycles \geq 3, guadecitabine was given for 5 days only (60 mg/m²/day, Days 1-5).

Arm title	Treatment Choice
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Arm description:

Intermediate or high dose cytarabine (HiDAC), MEC, FLAG/FLAG-Ida, LDAC, decitabine, azacitidine, or best supportive care (BSC) only.

Arm type	Active comparator
Investigational medicinal product name	Various treatment choice products
Investigational medicinal product code	
Other name	cytarabine, mitoxantrone, etoposide, fludarabine, idarubicin, decitabine, azacitidine
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

High intensity: Intermediate or high dose cytarabine (HiDAC), recommended as 1-1.5 g/m² every 12 hours or up to 6 g/m²/day for \leq 6 days, maximum 36 g/m² per cycle; MEC: For example: mitoxantrone 6-12 mg/m² IV (recommended 8 mg/m²), etoposide 80-200 mg/m² IV (recommended 100 mg/m²), and cytarabine 1000 mg/m² IV; each daily for 5 days (Days 1-5); FLAG/FLAG-Ida: For example: fludarabine 25-30 mg/m² IV daily Days 1-5; cytarabine 1-2 g/m² IV daily for up to 5 days (recommended to be given for 4 hours after fludarabine); G-CSF SC daily from Day 6 up to white cell count recovery with or without idarubicin 8 mg/m² IV daily on Days 3 to 5.

Low intensity: LDAC 20 mg SC or IV twice daily on Days 1-10; Decitabine 20 mg/m² IV daily on Days 1-5; Azacitidine 75 mg/m² IV or SC daily on Days 1-7.

Best supportive care only.

Number of subjects in period 1	Guadacitabine	Treatment Choice
Started	148	154
Completed	28	20
Not completed	120	134
Consent withdrawn by subject	3	6
Death	117	127
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Guadacitabine
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Reporting group description:

Guadacitabine was administered subcutaneously (SC) at a dose of 60 mg/m² in 28-day cycles.

Reporting group title	Treatment Choice
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Reporting group description:

Intermediate or high dose cytarabine (HiDAC), MEC, FLAG/FLAG-Ida, LDAC, decitabine, azacitidine, or best supportive care (BSC) only.

Reporting group values	Guadacitabine	Treatment Choice	Total
Number of subjects	148	154	302
Age categorical			
Units: Subjects			
Adults (18-64 years)	72	92	164
From 65-84 years	76	62	138
Age continuous			
Units: years			
arithmetic mean	61.8	59.8	
standard deviation	± 12.2	± 13.1	-
Gender categorical			
Units: Subjects			
Female	62	76	138
Male	86	78	164

End points

End points reporting groups

Reporting group title	Guadacitabine
Reporting group description: Guadacitabine was administered subcutaneously (SC) at a dose of 60 mg/m ² in 28-day cycles.	
Reporting group title	Treatment Choice
Reporting group description: Intermediate or high dose cytarabine (HiDAC), MEC, FLAG/FLAG-Ida, LDAC, decitabine, azacitidine, or best supportive care (BSC) only.	
Subject analysis set title	Guadecitabine vs Treatment Choice
Subject analysis set type	Sub-group analysis
Subject analysis set description: Arm comparison	

Primary: Overall survival

End point title	Overall survival
End point description: Number of days from date of randomization to date of death	
End point type	Primary
End point timeframe: From the date of randomization until the date of death, or approximately 30 months	

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Days				
median (confidence interval 95%)	191 (141 to 253)	163 (131 to 213)		

Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description: OS between guadecitabine vs. treatment choice using stratified log-rank test. Due to pre-specified hierarchical testing plan, other endpoints were not evaluated for statistical significance.	
Comparison groups	Guadacitabine v Treatment Choice
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3287
Method	Stratified log-rank

Secondary: Event free survival

End point title	Event free survival
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End point description:

Number of days from randomization to the earliest date of treatment discontinuation (for reasons other than initiation of hematopoietic cell transplant [HCT]), start of alternative anti-leukemia therapy (except for HCT), or death

End point type	Secondary
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End point timeframe:

From the date of randomization until treatment discontinuation, or approximately 23 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Days				
median (confidence interval 95%)	90 (73 to 105)	71.5 (53 to 78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Long-term survival

End point title	Long-term survival
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End point description:

Survival rate at 1 year after randomization; subjects were also be followed to estimate 2-year survival rate

End point type	Secondary
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End point timeframe:

Up to approximately 30 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Proportion				
number (confidence interval 95%)				
12-month survival rate	0.32 (0.25 to 0.40)	0.26 (0.20 to 0.34)		
24-month survival rate	0.19 (0.12 to 0.26)	0.10 (0.05 to 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days alive and out of the hospital

End point title	Number of days alive and out of the hospital
End point description: Number of days alive and out of the hospital	
End point type	Secondary
End point timeframe: 6 months	

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Days				
least squares mean (confidence interval 95%)	73.2 (53.2 to 93.2)	73.9 (53.8 to 94.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Transfusion independence

End point title	Transfusion independence
End point description: Number of subjects without red blood cell (RBC) or platelet transfusion for any period of 8 weeks after treatment divided by the total number of subjects included in the efficacy analysis	
End point type	Secondary
End point timeframe: Baseline up to approximately 26 months	

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Percentage of subjects				
number (not applicable)				
Overall transfusion independence	20.3	13.0		
Platelet transfusion independence	23.6	21.4		
RBC transfusion independence	21.6	14.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete response and complete response with partial hematologic recovery

End point title	Complete response and complete response with partial hematologic recovery
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End point description:

Number of subjects with complete response (CR) and CR with partial hematologic recovery divided by the total number of subjects included in the efficacy analysis

End point type	Secondary
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End point timeframe:

Baseline to end of treatment, or approximately 26 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Percentage of subjects				
number (not applicable)	16.9	7.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Composite complete response (CRc)

End point title	Composite complete response (CRc)
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End point description:

Number of subjects with complete response plus CR with incomplete blood count recovery (CRi) plus CR with incomplete platelet recovery (CRp) divided by the total number of subjects included in the efficacy analysis

End point type	Secondary
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End point timeframe:

Baseline to end of treatment, or approximately 26 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Percentage of subjects				
number (not applicable)	27.0	14.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Hematopoietic cell transplant (HCT)

End point title	Hematopoietic cell transplant (HCT)
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End point description:

Number of subjects who underwent HCT divided by the total number of subjects included in the efficacy analysis

End point type	Secondary
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End point timeframe:

Baseline to end of treatment, or approximately 26 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	154		
Units: Percentage of subjects				
number (not applicable)	17.6	16.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of combined CR and CRh

End point title	Duration of combined CR and CRh
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End point description:

Time from first CR or CRh to time of relapse; the date of the earliest of the following 3 events: (1) relapse (defined as the earliest time point whereby BM assessment or PB assessment by the investigator indicate relapse/disease progression due to confirmed reappearance of leukemic blasts in PB or $\geq 5\%$ leukemic blasts in BM, or clinical progression determined by the investigator), (2) start of alternative therapy (except HCT) or (3) death

End point type	Secondary
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End point timeframe:

Baseline to end of treatment, or approximately 26 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	12		
Units: Days				
median (confidence interval 95%)	124 (73 to 315)	63 (8 to 71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events

End point title	Incidence of adverse events
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End point description:

Number of subjects with any adverse event (AE) divided by the total number of subjects included in the safety analysis

End point type	Secondary
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End point timeframe:

From first dose until 30 days after the last dose of study drug, or approximately 26 months

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	147		
Units: Percentage of subjects				
number (not applicable)	96.6	97.3		

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause mortality

End point title	All-cause mortality
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End point description:

All-cause mortality in the first 30 days and first 60 days after the start of treatment divided by the total number of subjects receiving at least one dose of study treatment

End point type	Secondary
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End point timeframe:

From the first dose until 60 days after the first dose of study drug

End point values	Guadacitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	147		
Units: Percentage of subjects				
number (not applicable)				
Within 30 days	11.7	9.5		
Within 60 days	24.8	20.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EQ-5D-5L Index Score

End point title	Change in EQ-5D-5L Index Score
End point description:	
Change from baseline in EQ-5D-5L index scores in the first 6 months; index score is calculated based on a 5 point scoring scale where scores range from -0.281 (for the worst health state, score of 5 for all categories) to 1 (for the best health state, score of 1 for all categories).	
End point type	Secondary
End point timeframe:	
Baseline to 6 months	

End point values	Guadacitabine	Treatment Choice	Guadecitabine vs Treatment Choice	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	148	154		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Cycle 2 Day 1	-0.027 (-0.061 to 0.007)	-0.034 (-0.068 to 0.001)	0.006 (-0.042 to 0.055)	
Cycle 3 Day 1	-0.026 (-0.063 to 0.011)	-0.028 (-0.066 to 0.010)	0.002 (-0.051 to 0.055)	
Cycle 4 Day 1	-0.008 (-0.050 to 0.034)	-0.061 (-0.108 to -0.015)	0.053 (-0.010 to 0.116)	
Cycle 5 Day 1	-0.022 (-0.072 to 0.027)	-0.072 (-0.126 to -0.019)	0.050 (-0.023 to 0.123)	
Cycle 6 Day 1	-0.027 (-0.071 to 0.017)	-0.070 (-0.188 to -0.022)	0.043 (-0.022 to 0.108)	
Cycle 7 Day 1	-0.020 (-0.071 to 0.030)	-0.022 (-0.076 to 0.033)	0.002 (-0.073 to 0.076)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EQ-5D-5L Visual Analogue Scale Score

End point title	Change in EQ-5D-5L Visual Analogue Scale Score
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End point description:

Change from baseline in EQ-5D-5L visual analogue scale (VAS) score in the first 6 months; VAS score is obtained using vertical 20-cm visual analogue scale with the top value of 100 labelled as 'the best health you can imagine' and the bottom value of 0 labelled as 'the worst health you can imagine'

End point type	Secondary
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End point timeframe:

Baseline to 6 months

End point values	Guadacitabine	Treatment Choice	Guadecitabine vs Treatment Choice	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	148	154		
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Cycle 2 Day 1	-2.80 (-6.26 to 0.65)	-1.86 (-5.40 to 1.67)	-0.94 (-5.88 to 4.00)	
Cycle 3 Day 1	-0.61 (-4.08 to 2.87)	-1.47 (-5.02 to 2.08)	0.86 (-4.11 to 5.83)	
Cycle 4 Day 1	1.13 (-2.24 to 4.51)	-2.37 (-6.04 to 1.29)	3.51 (-1.48 to 8.49)	
Cycle 5 Day 1	1.28 (-2.88 to 5.44)	-2.30 (-6.83 to 2.22)	3.58 (-2.57 to 9.72)	
Cycle 6 Day 1	0.67 (-3.51 to 4.85)	-1.42 (-6.04 to 3.21)	2.09 (-4.14 to 8.32)	
Cycle 7 Day 1	-0.44 (-5.66 to 4.78)	-0.77 (-6.46 to 4.93)	0.33 (-7.40 to 8.05)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to approximately 26 months

Adverse event reporting additional description:

Adverse events are recorded from the start of study treatment until 30 days after the last dose of study treatment or until the subject starts a new anti-AML treatment, whichever occurs first. Guadacitabine subjects received a median of 3.0 cycles (range 1-24) and TC subjects received a median of 2.0 cycles (range 1-17).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Guadacitabine
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Reporting group description:

Guadacitabine was administered subcutaneously (SC) at a dose of 60 mg/m² in 28-day cycles.

Reporting group title	Treatment Choice
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Reporting group description:

Intermediate or high dose cytarabine (HiDAC), MEC, FLAG/FLAG-Ida, LDAC, decitabine, azacitidine, or best supportive care (BSC) only.

Serious adverse events	Guadacitabine	Treatment Choice	
Total subjects affected by serious adverse events			
subjects affected / exposed	113 / 145 (77.93%)	91 / 147 (61.90%)	
number of deaths (all causes)	114	126	
number of deaths resulting from adverse events	40	30	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 145 (1.38%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	5 / 145 (3.45%)	6 / 147 (4.08%)	
occurrences causally related to treatment / all	1 / 5	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 145 (2.07%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infiltration			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 145 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	2 / 145 (1.38%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (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 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (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			
Anaphylactic transfusion reaction subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory distress			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (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	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	4 / 145 (2.76%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	

Cardiac failure			
subjects affected / exposed	3 / 145 (2.07%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac failure acute			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 145 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	0 / 145 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	2 / 145 (1.38%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	4 / 145 (2.76%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	4 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	41 / 145 (28.28%)	33 / 147 (22.45%)	
occurrences causally related to treatment / all	33 / 67	11 / 42	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 145 (2.07%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal mucosal tear			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral mucosal erythema			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland enlargement			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	2 / 145 (1.38%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue oedema			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (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	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 145 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anal abscess			
subjects affected / exposed	2 / 145 (1.38%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	4 / 145 (2.76%)	5 / 147 (3.40%)	
occurrences causally related to treatment / all	1 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholinitis			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	4 / 145 (2.76%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 145 (2.76%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Corynebacterium bacteraemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermo-hypodermatitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	4 / 145 (2.76%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated varicella zoster vaccine virus infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecthyma			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear cellulitis			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective myositis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal sepsis			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucormycosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus B19 infection			

subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	27 / 145 (18.62%)	25 / 147 (17.01%)	
occurrences causally related to treatment / all	9 / 31	7 / 32	
deaths causally related to treatment / all	1 / 6	2 / 8	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 145 (1.38%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	15 / 145 (10.34%)	16 / 147 (10.88%)	
occurrences causally related to treatment / all	6 / 18	5 / 16	
deaths causally related to treatment / all	0 / 4	3 / 7	
Septic shock			
subjects affected / exposed	7 / 145 (4.83%)	5 / 147 (3.40%)	
occurrences causally related to treatment / all	2 / 8	4 / 7	
deaths causally related to treatment / all	0 / 3	1 / 2	
Sinusitis fungal			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (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	0 / 145 (0.00%)	3 / 147 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	2 / 145 (1.38%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			

subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 145 (1.38%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 145 (0.69%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Guadacitabine	Treatment Choice	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	138 / 145 (95.17%)	137 / 147 (93.20%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 145 (10.34%)	4 / 147 (2.72%)	
occurrences (all)	20	4	
Hypotension			
subjects affected / exposed	19 / 145 (13.10%)	11 / 147 (7.48%)	
occurrences (all)	20	14	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 145 (7.59%)	15 / 147 (10.20%)	
occurrences (all)	15	20	
Fatigue			
subjects affected / exposed	20 / 145 (13.79%)	27 / 147 (18.37%)	
occurrences (all)	23	32	
Injection site reaction			
subjects affected / exposed	29 / 145 (20.00%)	12 / 147 (8.16%)	
occurrences (all)	35	12	
Oedema peripheral			
subjects affected / exposed	23 / 145 (15.86%)	23 / 147 (15.65%)	
occurrences (all)	28	28	
Pyrexia			
subjects affected / exposed	33 / 145 (22.76%)	36 / 147 (24.49%)	
occurrences (all)	50	50	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 145 (15.17%)	27 / 147 (18.37%)	
occurrences (all)	28	31	
Dyspnoea			
subjects affected / exposed	20 / 145 (13.79%)	17 / 147 (11.56%)	
occurrences (all)	21	18	
Epistaxis			

subjects affected / exposed occurrences (all)	16 / 145 (11.03%) 22	16 / 147 (10.88%) 30	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 145 (2.76%) 8	9 / 147 (6.12%) 9	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	14 / 145 (9.66%) 16	13 / 147 (8.84%) 14	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	12 / 145 (8.28%) 15	7 / 147 (4.76%) 15	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	11 / 145 (7.59%) 13	8 / 147 (5.44%) 12	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	6 / 145 (4.14%) 6	8 / 147 (5.44%) 15	
Blood bilirubin increased subjects affected / exposed occurrences (all)	8 / 145 (5.52%) 14	9 / 147 (6.12%) 11	
Blood creatinine increased subjects affected / exposed occurrences (all)	8 / 145 (5.52%) 11	4 / 147 (2.72%) 6	
Weight decreased subjects affected / exposed occurrences (all)	5 / 145 (3.45%) 6	9 / 147 (6.12%) 10	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	11 / 145 (7.59%) 11	6 / 147 (4.08%) 7	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	8 / 145 (5.52%) 9	11 / 147 (7.48%) 14	

Headache			
subjects affected / exposed	30 / 145 (20.69%)	20 / 147 (13.61%)	
occurrences (all)	39	26	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	37 / 145 (25.52%)	41 / 147 (27.89%)	
occurrences (all)	68	108	
Febrile neutropenia			
subjects affected / exposed	25 / 145 (17.24%)	29 / 147 (19.73%)	
occurrences (all)	32	35	
Leukopenia			
subjects affected / exposed	14 / 145 (9.66%)	14 / 147 (9.52%)	
occurrences (all)	23	19	
Neutropenia			
subjects affected / exposed	47 / 145 (32.41%)	28 / 147 (19.05%)	
occurrences (all)	87	55	
Thrombocytopenia			
subjects affected / exposed	43 / 145 (29.66%)	46 / 147 (31.29%)	
occurrences (all)	77	137	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 145 (7.59%)	11 / 147 (7.48%)	
occurrences (all)	12	16	
Constipation			
subjects affected / exposed	33 / 145 (22.76%)	33 / 147 (22.45%)	
occurrences (all)	36	42	
Diarrhoea			
subjects affected / exposed	36 / 145 (24.83%)	32 / 147 (21.77%)	
occurrences (all)	46	40	
Dyspepsia			
subjects affected / exposed	12 / 145 (8.28%)	5 / 147 (3.40%)	
occurrences (all)	12	5	
Haemorrhoids			
subjects affected / exposed	11 / 145 (7.59%)	9 / 147 (6.12%)	
occurrences (all)	12	9	
Nausea			

subjects affected / exposed occurrences (all)	42 / 145 (28.97%) 58	38 / 147 (25.85%) 52	
Stomatitis subjects affected / exposed occurrences (all)	16 / 145 (11.03%) 21	20 / 147 (13.61%) 21	
Vomiting subjects affected / exposed occurrences (all)	24 / 145 (16.55%) 35	20 / 147 (13.61%) 33	
Skin and subcutaneous tissue disorders			
Petechiae subjects affected / exposed occurrences (all)	12 / 145 (8.28%) 13	7 / 147 (4.76%) 8	
Rash subjects affected / exposed occurrences (all)	11 / 145 (7.59%) 12	9 / 147 (6.12%) 17	
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	8 / 145 (5.52%) 9	2 / 147 (1.36%) 2	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	12 / 145 (8.28%) 14	10 / 147 (6.80%) 11	
Back pain subjects affected / exposed occurrences (all)	15 / 145 (10.34%) 16	12 / 147 (8.16%) 13	
Myalgia subjects affected / exposed occurrences (all)	8 / 145 (5.52%) 9	5 / 147 (3.40%) 5	
Pain in extremity subjects affected / exposed occurrences (all)	11 / 145 (7.59%) 15	7 / 147 (4.76%) 13	
Infections and infestations			
Oral herpes subjects affected / exposed occurrences (all)	8 / 145 (5.52%) 8	5 / 147 (3.40%) 5	

Pneumonia subjects affected / exposed occurrences (all)	15 / 145 (10.34%) 16	14 / 147 (9.52%) 17	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	27 / 145 (18.62%) 32	20 / 147 (13.61%) 24	
Hyperkalaemia subjects affected / exposed occurrences (all)	9 / 145 (6.21%) 11	3 / 147 (2.04%) 8	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	10 / 145 (6.90%) 12	7 / 147 (4.76%) 8	
Hypocalcaemia subjects affected / exposed occurrences (all)	9 / 145 (6.21%) 12	5 / 147 (3.40%) 5	
Hypokalaemia subjects affected / exposed occurrences (all)	29 / 145 (20.00%) 47	38 / 147 (25.85%) 63	
Hypomagnesaemia subjects affected / exposed occurrences (all)	14 / 145 (9.66%) 26	16 / 147 (10.88%) 25	
Hyponatraemia subjects affected / exposed occurrences (all)	10 / 145 (6.90%) 19	3 / 147 (2.04%) 4	
Hypophosphataemia subjects affected / exposed occurrences (all)	13 / 145 (8.97%) 21	9 / 147 (6.12%) 20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2017	<ul style="list-style-type: none">• Incorporated the changes from previous region-specific amendments• Clarified clinical response assessment using bone marrow and peripheral blood samples.• Clarified inclusion and exclusion criteria.• Clarified what was meant by "alternative anti-leukemia therapy" in this protocol and when the safety follow-up visit was to be performed.• Provided information and references on cytogenetics-based risk classification.• Amended the timing of the planned primary analysis of overall survival if the number of death events had not occurred within a reasonable duration.• Clarified when electrocardiogram (ECG) and vital sign safety assessments were performed for subjects in the BSC group.• Clarified long-term follow-up procedures.• Implemented administrative updates.
14 February 2018	<ul style="list-style-type: none">• Added the efficacy variable "complete response with partial hematological recovery (CRh)" based on recent Food and Drug Administration (FDA) marketing approvals for relapsed/refractory (r/r) AML treatments based on this variable.• Combined CRh with CR for calculation of duration of response to include important response criteria in the duration calculation.• Allowed subjects randomly assigned to guadecitabine to receive hydroxyurea in the first 30 days of treatment to enable subjects to receive at least 2 cycles of study treatment, as guadecitabine may not adequately control proliferative disease from one cycle only.• Excluded subjects with high PB blasts >50% AND poor ECOG PS of 2, which indicates highly aggressive proliferative disease, as subjects may be at imminent risk of death.• Clarified that, after discontinuing study treatment, subjects should not withdraw consent just because they wished to participate in another experimental study.• Allowed the 10-day regimen of guadecitabine to be given on Days 1-10 (rather than Days 1-5 and 8-12) to facilitate quicker control of apparent progression in the first 2 cycles.• Allowed concomitant intrathecal treatment to control central nervous system (CNS) disease, as study treatment is not active in CNS disease.• Allowed donor lymphocytes infusion (DLI) if it was part of standard practice in certain subjects with r/r AML.
29 October 2018	<ul style="list-style-type: none">• Study closed to further enrollment based on recommendation from DMC.• Revised plan for interim analysis to describe futility analysis.• Specified study follow-up stop date to be Q3 2019 or when the last subject was off study and removed provision for subjects to continue receiving guadecitabine after study completion.• Administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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12 September 2018	Based on data from 278 randomly assigned subjects, the Data Monitoring Committee (DMC) recommended to stop further enrollment into the trial based on futility analysis that showed the trial was unlikely to show superiority of guadecitabine over treatment choice (TC) for the primary endpoint of overall survival (OS). Consequently, the study was closed to further enrollment in September 2018 (Amendment 4).	-
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Notes:

Limitations and caveats

None reported