Clinical trial results:
A Phase 3, Multicenter, Randomized, Open-Label Study of Guadecitabine (SGI-110) versus Treatment Choice in Adults with Myelodysplastic Syndromes (MDS) or Chronic Myelomonocytic Leukemia (CMML) Previously Treated with Hypomethylating Agent

Summary

EudraCT number	2015-005257-12
Trial protocol	BE DE CZ ES PL DK SE
Global end of trial date	30 November 2020

Results information

Result version number	v1
This version publication date	17 December 2021
First version publication date	17 December 2021

Trial information

Trial identification

Sponsor protocol code	SGI-110-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02907359
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astex Pharmaceuticals, Inc
Sponsor organisation address	4420 Rosewood Drive, Suite 200, Pleasanton, United States, CA 94588
Public contact	Astex Pharmaceuticals, Inc, Astex Pharmaceuticals, Inc, SGI-110-07@astx.com
Scientific contact	SGI-110-07 study mailbox, SGI-110-07 study mailbox, SGI-110-07@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	30 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to assess and compare overall survival (OS) between guadecitabine and treatment choice (TC) in adults with MDS or CMML previously treated with a hypomethylating agent (azacitidine or decitabine, or both).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	38 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Japan: 71
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	United States: 125
Country: Number of subjects enrolled	Belgium: 13
Worldwide total number of subjects	417
EEA total number of subjects	166

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)	34
From 65 to 84 years	370
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 101 investigative sites in the United States, Canada, Spain, Italy, France, Germany, Czech Republic, Denmark, Poland, Belgium, Sweden, United Kingdom, Japan, South Korea from 13 January 2017 to 30 November 2020.

Pre-assignment

Screening details:

A total of 417 subjects were randomised (277 in Guadecitabine arm group and 140 in Treatment Choice arm group) and 392 received treatment. Of 417 subjects, 48 completed the study.

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	Guadecitabine

Arm description:

Subjects received Guadecitabine 60 milligrams per square meter (mg/m^2), subcutaneously (SC), on Days 1-5 of each 28-day cycle for at least 6 cycles in the absence of unacceptable toxicity or disease progression requiring alternative therapy. Subjects received Guadecitabine treatment beyond 6 cycles as long as the subject continued to benefit based on investigator judgment and subject response and tolerability.

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

Dosage and administration details:

Guadecitabine 60 mg/m^2 was administered as subcutaneous injection on Days 1-5 of each 28-day cycle.

Arm title	Treatment Choice

Arm description:

Subjects received one of the three treatment choice: 1) Low dose cytarabine (LDAC) 20 mg/m^2 SC or intravenous (IV) once daily for 14 days of each 28-day cycles for at least 4 cycles. 2) Standard Intensive Chemotherapy (IC) of a 7+3 regimen: (Cytarabine 100-200 mg/m^2/day given as continuous infusion for 7 days and an anthracycline (daunorubicin (45-60 mg)/idarubicin (9-12 mg)/mitoxantrone (8-12 mg)/m^2 by intravenous infusion for 3 days. 3) Best Supportive Care (BSC) included, but was not limited to, blood transfusions (Red blood cells [RBCs] or platelets), growth factors including erythropoiesis stimulating agents, granulocyte stimulating factors, iron chelating therapy, and broad-spectrum antibiotics and/or antifungals. Duration for treatment choice was as per locally approved prescribing information and institutional standard practice.

Arm type	Active comparator
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Low dose cytarabine (LDAC) 20 mg/m^2 SC or IV once daily for 14 days of each 28-day cycles for at

least 4 cycles; or cytarabine 100-200 mg/m^2/day given as continuous infusion for 7 days as part of Standard Intensive Chemotherapy (IC) of a 7+3 regimen.

Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Mitoxantrone was given 8-12 mg/m^2 by intravenous infusion for 3 days as part of Standard Intensive Chemotherapy (IC) of a 7+3 regimen.

Investigational medicinal product name	Idarubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Idarubicin was given 9-12 mg/m^2 by intravenous infusion for 3 days as part of Standard Intensive Chemotherapy (IC) of a 7+3 regimen.

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daunorubicin was given 45-60 mg/m^2 by intravenous infusion for 3 days as part of Standard Intensive Chemotherapy (IC) of a 7+3 regimen.

Number of subjects in period 1	Guadecitabine	Treatment Choice
Started	277	140
Safety Population	270	122
Completed	36	12
Not completed	241	128
Death	234	117
Withdrawal by Subject	6	11
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Guadecitabine
Reporting group description:	
Subjects received Guadecitabine 60 milligrams per square meter (mg/m^2), subcutaneously (SC), on Days 1-5 of each 28-day cycle for at least 6 cycles in the absence of unacceptable toxicity or disease progression requiring alternative therapy. Subjects received Guadecitabine treatment beyond 6 cycles as long as the subject continued to benefit based on investigator judgment and subject response and tolerability.	
Reporting group title	Treatment Choice
Reporting group description:	
Subjects received one of the three treatment choice: 1) Low dose cytarabine (LDAC) 20 mg/m^2 SC or intravenous (IV) once daily for 14 days of each 28-day cycles for at least 4 cycles. 2) Standard Intensive Chemotherapy (IC) of a 7+3 regimen: (Cytarabine 100-200 mg/m^2/day given as continuous infusion for 7 days and an anthracycline (daunorubicin (45-60 mg)/idarubicin (9-12 mg)/mitoxantrone (8-12 mg)/m^2 by intravenous infusion for 3 days. 3) Best Supportive Care (BSC) included, but was not limited to, blood transfusions (Red blood cells [RBCs] or platelets), growth factors including erythropoiesis stimulating agents, granulocyte stimulating factors, iron chelating therapy, and broad-spectrum antibiotics and/or antifungals. Duration for treatment choice was as per locally approved prescribing information and institutional standard practice.	

Reporting group values	Guadecitabine	Treatment Choice	Total
Number of subjects	277	140	417
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	73.5	73.7	
standard deviation	± 7.0	± 6.1	-
Gender categorical Units: Subjects			
Male	194	96	290
Female	83	44	127
Ethnicity Units: Subjects			
Hispanic or Latino	24	7	31
Not Hispanic or Latino	225	117	342
Not Reported	28	16	44
Race Units: Subjects			
White	179	86	265
Black or African American	5	3	8
Asian	64	33	97
American Indian or Alaska Native	0	1	1
Native Hawaiian or Other Pacific Islander	0	1	1
Not Reported	29	16	45

End points

End points reporting groups

Reporting group title	Guadecitabine

Reporting group description:

Subjects received Guadecitabine 60 milligrams per square meter (mg/m^2), subcutaneously (SC), on Days 1-5 of each 28-day cycle for at least 6 cycles in the absence of unacceptable toxicity or disease progression requiring alternative therapy. Subjects received Guadecitabine treatment beyond 6 cycles as long as the subject continued to benefit based on investigator judgment and subject response and tolerability.

Reporting group title	Treatment Choice

Reporting group description:

Subjects received one of the three treatment choice: 1) Low dose cytarabine (LDAC) 20 mg/m^2 SC or intravenous (IV) once daily for 14 days of each 28-day cycles for at least 4 cycles. 2) Standard Intensive Chemotherapy (IC) of a 7+3 regimen: (Cytarabine 100-200 mg/m^2/day given as continuous infusion for 7 days and an anthracycline (daunorubicin (45-60 mg)/idarubicin (9-12 mg)/mitoxantrone (8-12 mg)/m^2 by intravenous infusion for 3 days. 3) Best Supportive Care (BSC) included, but was not limited to, blood transfusions (Red blood cells [RBCs] or platelets), growth factors including erythropoiesis stimulating agents, granulocyte stimulating factors, iron chelating therapy, and broad-spectrum antibiotics and/or antifungals. Duration for treatment choice was as per locally approved prescribing information and institutional standard practice.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the number of days from the day the subject was randomised to the date of death due to any cause. Survival time was censored on the last date the subject is known alive with no event of death. Efficacy Analysis Set included all subjects randomly assigned to study treatment.

End point type	Primary

End point timeframe:

From randomisation up to death (up to approximately 38 months)

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: days				
median (confidence interval 95%)	277.0 (243.0 to 313.0)	252.0 (200.0 to 325.0)		

Statistical analyses

Statistical analysis title	Guadecitabine vs Treatment Choice

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	Guadecitabine v Treatment Choice

Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6063 [1]
Method	Stratified Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.19

Notes:

[1] - The stratification factors include disease category (MDS vs CMML), baseline BM blasts (>10% vs ≤10%), TC option (LDAC vs IC vs BSC), and study center region (North America vs Rest of the world {ROW}).

Secondary: Percentage of Subjects with Transfusion Independence for 8 weeks

End point title	Percentage of Subjects with Transfusion Independence for 8 weeks

End point description:

Transfusion independence rate was calculated as the number of subjects with neither RBC nor platelet transfusion for any period of 8 weeks after the initiation of treatment (or cycle 1 day 1 {C1D1} visit date for subjects randomised to BSC or randomisation date for subjects not treated) and up to treatment discontinuation (or 180 days for subjects discontinuing the treatment within 6 months), while maintaining Haemoglobin (Hgb) ≥8 gram per decilitre (g/dL) and platelets ≥20×109/Litre (L) divided by the total number of subjects included in the efficacy analysis. Efficacy Analysis Set included all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 38 months

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: percentage of subjects				
number (not applicable)				
Transfusion Independence Rate (8 weeks)	15.9	15.7		
Platelet Transfusion Independence Rate	32.1	37.9		
RBC Transfusion Independence Rate	22.4	20.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved Marrow Complete Response (mCR) with Transfusion Independence Rate

End point title	Percentage of Subjects who Achieved Marrow Complete

	Response (mCR) with Transfusion Independence Rate

End point description:

mCR was defined as per 2006 MDS IWG criteria as reduction of bone marrow blasts to ≤5% and decrease by 50% or more with or without normalization of peripheral counts. Transfusion independence rate was calculated as the number of subjects with neither RBC nor platelet transfusion for any period of 8 weeks after the initiation of treatment (or C1D1 visit date for subjects randomised to BSC or randomisation date for subjects not treated) and up to treatment discontinuation (or 180 days for subjects discontinuing the treatment within 6 months), while maintaining Hgb ≥8 g/dL and platelets ≥20×109/L divided by the total number of subjects included in the efficacy analysis. The percentage of subjects who achieved mCR and transfusion independence simultaneously in the same period were calculated for each group. Efficacy Analysis Set included all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 38 months

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: percentage of subjects				
number (not applicable)	5.8	2.9		

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 was defined as the number of days from randomisation to the earliest date when subjects have bone marrow (BM) or peripheral blood (PB) blasts ≥20%, conversion to acute myeloid leukemia (AML) or death of any cause. Subjects with no events in leukemia-free survival were censored on the last date of BM or PB blasts assessment, whichever is later. Efficacy Analysis Set included all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

From randomisation up to approximately 38 months

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: days				
median (confidence interval 95%)	173.0 (135.0 to 206.0)	181.0 (125.0 to 213.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Survival Rate at 1 Year After Randomisation

End point title	Survival Rate at 1 Year After Randomisation

End point description:

One year survival rate was defined as the percentage of subjects that survived at the end of the first year from randomisation. Subjects who did not have death in record were censored on the last date known to be alive. Efficacy Analysis Set included all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

From randomisation up to 12 months

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: percentage of subjects				
number (confidence interval 95%)	0.39 (0.34 to 0.45)	0.39 (0.30 to 0.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Alive and Out of The Hospital (NDAOH)

End point title	Number of Days Alive and Out of The Hospital (NDAOH)

End point description:

The date of each hospital admission and discharge was collected for each subject for up to 6 months, unless the subject died or withdrew consent prior to that time. Duration of each hospital stay in days was calculated as date of discharge minus date of admission. The NDAOH within first 6 month period was calculated as: NDAOH 6M=180 - total duration of all hospital stays within 180 days from the first treatment - number of death days before Day 180. For subjects who were lost to follow-up within 6 months, the NDAOH was calculated conservatively assuming that the subject would have died the day after the last contact day. Efficacy Analysis Set included all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Month 6

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: days				
median (full range (min-max))	144.0 (0 to 180)	149.5 (0 to 180)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Response (DR)

End point title	Disease Response (DR)

End point description:

DR: CR, PR, mCR, and HI (HI-E, HI-N, or HI-P) based on IWG 2006 criteria. CR: BM: ≤5% myeloblasts, Peripheral blood: Hgb≥11g/dL, Platelets (PLTs)≥100x10^9/L, Neutrophils≥1.0x10^9/L, Blasts 0%. PR: All CR criteria if abnormal before treatment except BM blasts decreased≥50% over pretreatment but still>5%, Cellularity, morphology not relevant. HI responses: 1) HI-E: Hgb increase≥1.5 g/dL, Relevant reduction of RBC units transfusions by absolute≥4 RBC transfusions/8 week(wk) compared with pretreatment transfusion number previous 8wk. Only RBC transfusions given for Hgb ≤9.0 g/dL. 2) HI-P: Absolute increase≥30x10^9/L starting>20x10^9/L PLTs; Increase from<20x10^9/L to>20x10^9/L and by≥100% 3) HI-N: ≥100% increase, absolute increase>0.5x10^9/L 4) Progression/relapse after HI: ≥1 of following: ≥50% decrement from maximum response levels in granulocytes/PLTs, Reduction in Hgb≥1.5 g/dL, Transfusion dependence. Efficacy Analysis Set included all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 38 months

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: percentage of subjects				
number (confidence interval 95%)				
Complete Response [CR]	1.4 (0.0 to 2.8)	0.7 (0.0 to 2.1)		
Partial Response [PR]	0 (0 to 0)	0 (0 to 0)		
Marrow Complete Response [mCR]	17.3 (12.9 to 21.8)	8.6 (3.9 to 13.2)		
Hematological Improvement [HI]	3.2 (1.2 to 5.3)	5.7 (1.9 to 9.6)		
HI with Erythroid (HI-E)	1.1 (0.0 to 2.2)	2.1 (0.0 to 4.5)		
HI with Platelet (HI-P)	1.8 (0.2 to 3.3)	2.1 (0.0 to 4.5)		
HI with Neutrophil (HI-N)	0.7 (0.0 to 1.7)	2.1 (0.0 to 4.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Response (CR)

End point title	Duration of Complete Response (CR)

End point description:

Duration of complete response (in number of days) was calculated from the first time a CR was observed to the date of the earliest of the following three events: 1) relapse/disease progression, 2) start of alternative therapy (except HCT) or 3) death. In the absence of any event, the duration of CR was censored at the last available time point (BM assessment, PB assessment, or safety/long-term follow-up visit) at which an event was not observed. Duration of complete response was analysed using a Kaplan-Meier method for subjects who achieved a CR during the study. CR: BM: ≤5% myeloblasts (all cell lines normal maturation), Peripheral blood: Hgb ≥11g/dL, PLTs ≥100x10^9/L, Neutrophils ≥1.0x10^9/L, Blasts 0%. Duration of response was reported for subjects with CR only. Here, 99999 indicates that upper and the lower limit of the median was not reached.

End point type	Secondary

End point timeframe:

Up to approximately 38 months

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: days				
median (confidence interval 95%)	198 (112.0 to 266.0)	406 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response, Complete Response (CR) and Best Response

End point title	Time to Response, Complete Response (CR) and Best Response

End point description:

Time to first response was defined as the time, in days, from the date of randomisation to the first date when any response was achieved. Time to CR was calculated as the time, in days, from the date of randomisation to the first date when CR was achieved. Time to best response was similarly defined as the time, in days, from the date of randomisation to the first date when a subject's best response, in the order of CR, PR, mCR or HI was achieved. Efficacy Analysis Set included all subjects randomly assigned to study treatment. n = number of subjects analysed for the given analysis.

End point type	Secondary

End point timeframe:

From study Day 1 to the earliest date that a response was first documented (Up to approximately 38

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: days				
median (full range (min-max))				
Time to First Response (n=61, 21)	63.0 (28 to 323)	67.0 (21 to 295)		
Time to CR (n=4, 1)	91.0 (56 to 106)	266 (266 to 266)		
Time to Best Response (n=61, 21)	64 (28 to 469)	77 (23 to 295)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Red Blood Cell (RBC) and Platelet Transfusions

End point title	Number of Red Blood Cell (RBC) and Platelet Transfusions

End point description:

The total number of red blood cells (RBCs) transfused or, separately, the total number of platelets transfused up to the 6-month time point for each subject was counted from the date of randomisation to Day 180, the date of last contact, or date of death, whichever occurred earlier. One RBC or platelet transfusion was defined as one unit, and a single bag of RBCs or platelets was considered one unit. Efficacy Analysis Set included all subjects randomly assigned to study treatment.

End point type	Secondary

End point timeframe:

Month 6

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: units				
arithmetic mean (standard deviation)				
RBC Transfusions	18.9 (± 13.94)	15.0 (± 13.53)		
Platelet Transfusions	16.8 (± 18.64)	12.1 (± 20.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-related Quality of Life (QOL) Scores By EuroQol 5-level 5-dimension (EQ-5D-5L) Score

End point title	Change From Baseline in Health-related Quality of Life (QOL) Scores By EuroQol 5-level 5-dimension (EQ-5D-5L) Score

End point description:

The EQ-5D-5L is a self-reported health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis. There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression used to obtain an Index Utility Score, as well as a visual analogue scale (VAS) that measures health state. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. Here negative change from Baseline indicates improvement in health status. Efficacy Analysis Set included all subjects randomly assigned to study treatment. n= number of subjects with data available at given time point.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=266, 119)	0.8414 (± 0.1596)	0.8404 (± 0.1587)		
Change from Baseline at Month 6 (n=103, 40)	-0.0386 (± 0.1466)	-0.0149 (± 0.1266)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-related QOL: EuroQOL Visual Analogue Scale (EQ-VAS) Score

End point title	Change From Baseline in Health-related QOL: EuroQOL Visual Analogue Scale (EQ-VAS) Score

End point description:

EQ VAS self-rating records the respondent's own assessment of his/her overall health status at time of completion, on a scale of 0 (worst health you can imagine) to 100 (best health you can imagine). Here negative change from Baseline indicates improvement in health status. Efficacy Analysis Set included all subjects randomly assigned to study treatment. n= number of subjects with data available at given time point.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	140		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=266, 119)	71.24 (± 18.33)	70.70 (± 18.32)		
Change from Baseline at Month 6 (n=103, 40)	-1.52 (± 16.39)	-2.43 (± 18.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects with Treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation subjects administered a drug; it does not necessarily have to have a causal relationship with this treatment. An SAE is defined any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalization; results in persistent or significant disability; is congenital anomaly; is suspected transmission of any infectious agent via a medicinal product or is medically important. Treatment emergent AEs which are those with onset date on or after the date of the first dose of study drug on C1D1 until 30 days after the last dose of study treatment, or the start of an alternative anticancer treatment, whichever occurs first. Safety Analysis Set included all subjects randomly assigned to study treatment who received any amount of study treatment or any component of a multi-dose study treatment regimen.

End point type	Secondary

End point timeframe:

From first dose through 30 days after last dose of study drug (up to approximately 46 months)

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	122		
Units: subjects				
number (not applicable)				
TEAE	268	113		
SAE	216	65		

Statistical analyses

No statistical analyses for this end point

Secondary: 30 and 60-day All-cause Mortality

End point title	30 and 60-day All-cause Mortality

End point description:

Number of deaths, regardless of cause, within 30 or 60 days from the first study dose divided by the total number of subjects included in the safety analysis set. Subjects who died within 30 days were also included in the 60-day mortality calculations. Safety Analysis Set included all subjects randomly assigned to study treatment who received any amount of study treatment or any component of a multi-dose study treatment regimen.

End point type	Secondary

End point timeframe:

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

End point values	Guadecitabine	Treatment Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	122		
Units: subjects				
number (not applicable)				
Within 30 Days	16	6		
Within 60 Days	35	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose through 30 days after last dose of study drug (up to approximately 46 months)

Adverse event reporting additional description:

Safety Analysis Set included all subjects randomly assigned to study treatment who received any amount of study treatment or any component of a multi-dose study treatment regimen. Total number of deaths (all causes): is presented for the safety population (participant flow shows number of deaths with primary reason for all randomised subjects).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Guadecitabine

Reporting group description:

Subjects received Guadecitabine 60 milligrams per square meter (mg/m^2), subcutaneous (SC), on Days 1-5 of each 28-day cycle for at least 6 cycles in the absence of unacceptable toxicity or disease progression requiring alternative therapy. Subjects received Guadecitabine treatment beyond 6 cycles as long as the subject continued to benefit based on investigator judgment and subject response and tolerability.

Reporting group title	Treatment Choice

Reporting group description:

Subjects received one of the three treatment choice: 1) Low dose cytarabine (LDAC) 20 mg/m^2 SC or intravenous (IV) once daily for 14 days of each 28-day cycles for at least 4 cycles. 2) Standard Intensive Chemotherapy (IC) of a 7+3 regimen: (Cytarabine 100-200 mg/m^2/day given as continuous infusion for 7 days and an anthracycline (daunorubicin (45-60 mg)/idarubicin (9-12 mg)/mitoxantrone (8-12 mg)/m^2 by intravenous infusion for 3 days. 3) Best Supportive Care (BSC) included, but was not limited to, blood transfusions (RBCs or platelets), growth factors including erythropoiesis stimulating agents, granulocyte stimulating factors, iron chelating therapy, and broad-spectrum antibiotics and/or antifungals. Duration for treatment choice was as per locally approved prescribing information and institutional standard practice.

Serious adverse events	Guadecitabine	Treatment Choice	
Total subjects affected by serious adverse events			
subjects affected / exposed	216 / 270 (80.00%)	65 / 122 (53.28%)	
number of deaths (all causes)	231	109	
number of deaths resulting from adverse events	58	20	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system leukaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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	1 / 270 (0.37%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Internal haemorrhage			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
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			
Pyrexia			
subjects affected / exposed	7 / 270 (2.59%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	1 / 8	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 270 (1.11%)	3 / 122 (2.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chest pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 270 (0.37%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 2	
Malaise			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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			
Epistaxis			
subjects affected / exposed	4 / 270 (1.48%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			

subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemothorax			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
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	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organic brain syndrome			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 270 (0.74%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute haemolytic transfusion reaction			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	0 / 270 (0.00%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Gastrointestinal arteriovenous malformation			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 270 (2.22%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	2 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 270 (1.48%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 270 (1.11%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 270 (0.74%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular extrasystoles			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	2 / 270 (0.74%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Cerebral haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
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	80 / 270 (29.63%)	19 / 122 (15.57%)	
occurrences causally related to treatment / all	72 / 141	11 / 26	
deaths causally related to treatment / all	1 / 4	0 / 1	
Thrombocytopenia			
subjects affected / exposed	8 / 270 (2.96%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	4 / 10	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	7 / 270 (2.59%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	4 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	3 / 270 (1.11%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	3 / 270 (1.11%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukostasis syndrome			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenic purpura			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agranulocytosis			

subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 270 (1.11%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	3 / 270 (1.11%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic gastritis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous ulcer			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			

subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
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	0 / 270 (0.00%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Retroperitoneal haematoma			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 270 (1.11%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute kidney injury			
subjects affected / exposed	1 / 270 (0.37%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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 / 270 (0.37%)	0 / 122 (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	3 / 270 (1.11%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula inflammation			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal chest pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
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	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	72 / 270 (26.67%)	17 / 122 (13.93%)	
occurrences causally related to treatment / all	51 / 97	2 / 21	
deaths causally related to treatment / all	7 / 15	0 / 5	
Sepsis			

subjects affected / exposed	26 / 270 (9.63%)	4 / 122 (3.28%)	
occurrences causally related to treatment / all	15 / 32	0 / 4	
deaths causally related to treatment / all	2 / 8	0 / 3	
Septic shock			
subjects affected / exposed	16 / 270 (5.93%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	2 / 16	1 / 2	
deaths causally related to treatment / all	1 / 9	0 / 0	
Cellulitis			
subjects affected / exposed	14 / 270 (5.19%)	2 / 122 (1.64%)	
occurrences causally related to treatment / all	10 / 22	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	11 / 270 (4.07%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	3 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	5 / 270 (1.85%)	3 / 122 (2.46%)	
occurrences causally related to treatment / all	1 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	4 / 270 (1.48%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infection			
subjects affected / exposed	4 / 270 (1.48%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Urosepsis			
subjects affected / exposed	4 / 270 (1.48%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			

subjects affected / exposed	3 / 270 (1.11%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Device related infection			
subjects affected / exposed	3 / 270 (1.11%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corynebacterium infection			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (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			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucormycosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising soft tissue infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (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	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal endocarditis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 270 (0.37%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection staphylococcal			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cellulitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			

subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium bacteraemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocardiosis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	2 / 270 (0.74%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	1 / 270 (0.37%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 122 (0.82%)	
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	Guadecitabine	Treatment Choice	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	266 / 270 (98.52%)	107 / 122 (87.70%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	15 / 270 (5.56%)	5 / 122 (4.10%)	
occurrences (all)	23	7	
Hypotension			
subjects affected / exposed	17 / 270 (6.30%)	3 / 122 (2.46%)	
occurrences (all)	19	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	53 / 270 (19.63%)	12 / 122 (9.84%)	
occurrences (all)	65	12	
Fatigue			
subjects affected / exposed	59 / 270 (21.85%)	11 / 122 (9.02%)	
occurrences (all)	75	12	
Injection site reaction			
subjects affected / exposed	46 / 270 (17.04%)	1 / 122 (0.82%)	
occurrences (all)	80	1	
Oedema peripheral			
subjects affected / exposed	42 / 270 (15.56%)	14 / 122 (11.48%)	
occurrences (all)	56	18	
Oedema			

subjects affected / exposed	14 / 270 (5.19%)	9 / 122 (7.38%)	
occurrences (all)	15	9	
Pyrexia			
subjects affected / exposed	60 / 270 (22.22%)	24 / 122 (19.67%)	
occurrences (all)	89	33	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	39 / 270 (14.44%)	8 / 122 (6.56%)	
occurrences (all)	48	10	
Dyspnoea			
subjects affected / exposed	33 / 270 (12.22%)	11 / 122 (9.02%)	
occurrences (all)	42	12	
Epistaxis			
subjects affected / exposed	44 / 270 (16.30%)	21 / 122 (17.21%)	
occurrences (all)	56	36	
Oropharyngeal pain			
subjects affected / exposed	14 / 270 (5.19%)	3 / 122 (2.46%)	
occurrences (all)	17	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	31 / 270 (11.48%)	5 / 122 (4.10%)	
occurrences (all)	32	5	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 270 (4.81%)	8 / 122 (6.56%)	
occurrences (all)	17	8	
Blood creatinine increased			
subjects affected / exposed	14 / 270 (5.19%)	5 / 122 (4.10%)	
occurrences (all)	16	8	
Weight decreased			
subjects affected / exposed	22 / 270 (8.15%)	6 / 122 (4.92%)	
occurrences (all)	27	6	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 270 (3.70%)	8 / 122 (6.56%)	
occurrences (all)	12	8	
Injury, poisoning and procedural			

complications			
Contusion			
subjects affected / exposed	24 / 270 (8.89%)	8 / 122 (6.56%)	
occurrences (all)	35	9	
Fall			
subjects affected / exposed	17 / 270 (6.30%)	5 / 122 (4.10%)	
occurrences (all)	20	5	
Transfusion reaction			
subjects affected / exposed	17 / 270 (6.30%)	3 / 122 (2.46%)	
occurrences (all)	66	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	34 / 270 (12.59%)	8 / 122 (6.56%)	
occurrences (all)	39	9	
Headache			
subjects affected / exposed	34 / 270 (12.59%)	9 / 122 (7.38%)	
occurrences (all)	42	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	63 / 270 (23.33%)	22 / 122 (18.03%)	
occurrences (all)	120	48	
Febrile neutropenia			
subjects affected / exposed	38 / 270 (14.07%)	6 / 122 (4.92%)	
occurrences (all)	70	6	
Neutropenia			
subjects affected / exposed	92 / 270 (34.07%)	19 / 122 (15.57%)	
occurrences (all)	276	20	
Leukopenia			
subjects affected / exposed	32 / 270 (11.85%)	12 / 122 (9.84%)	
occurrences (all)	64	13	
Thrombocytopenia			
subjects affected / exposed	84 / 270 (31.11%)	25 / 122 (20.49%)	
occurrences (all)	278	66	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 270 (10.00%)	6 / 122 (4.92%)	
occurrences (all)	28	8	

Diarrhoea			
subjects affected / exposed	60 / 270 (22.22%)	20 / 122 (16.39%)	
occurrences (all)	78	23	
Constipation			
subjects affected / exposed	62 / 270 (22.96%)	12 / 122 (9.84%)	
occurrences (all)	79	17	
Nausea			
subjects affected / exposed	43 / 270 (15.93%)	15 / 122 (12.30%)	
occurrences (all)	66	22	
Haemorrhoids			
subjects affected / exposed	16 / 270 (5.93%)	4 / 122 (3.28%)	
occurrences (all)	16	4	
Stomatitis			
subjects affected / exposed	38 / 270 (14.07%)	7 / 122 (5.74%)	
occurrences (all)	50	10	
Vomiting			
subjects affected / exposed	29 / 270 (10.74%)	7 / 122 (5.74%)	
occurrences (all)	36	9	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	14 / 270 (5.19%)	2 / 122 (1.64%)	
occurrences (all)	19	2	
Petechiae			
subjects affected / exposed	24 / 270 (8.89%)	2 / 122 (1.64%)	
occurrences (all)	29	3	
Rash			
subjects affected / exposed	27 / 270 (10.00%)	7 / 122 (5.74%)	
occurrences (all)	34	9	
Pruritus			
subjects affected / exposed	19 / 270 (7.04%)	2 / 122 (1.64%)	
occurrences (all)	19	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 270 (6.67%)	5 / 122 (4.10%)	
occurrences (all)	20	6	
Musculoskeletal pain			

subjects affected / exposed	17 / 270 (6.30%)	2 / 122 (1.64%)	
occurrences (all)	21	2	
Pain in extremity			
subjects affected / exposed	15 / 270 (5.56%)	7 / 122 (5.74%)	
occurrences (all)	18	7	
Back pain			
subjects affected / exposed	33 / 270 (12.22%)	3 / 122 (2.46%)	
occurrences (all)	40	5	
Infections and infestations			
Cellulitis			
subjects affected / exposed	22 / 270 (8.15%)	4 / 122 (3.28%)	
occurrences (all)	30	4	
Nasopharyngitis			
subjects affected / exposed	10 / 270 (3.70%)	7 / 122 (5.74%)	
occurrences (all)	11	8	
Pneumonia			
subjects affected / exposed	40 / 270 (14.81%)	8 / 122 (6.56%)	
occurrences (all)	50	11	
Upper respiratory tract infection			
subjects affected / exposed	16 / 270 (5.93%)	7 / 122 (5.74%)	
occurrences (all)	21	7	
Urinary tract infection			
subjects affected / exposed	13 / 270 (4.81%)	7 / 122 (5.74%)	
occurrences (all)	14	8	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	45 / 270 (16.67%)	6 / 122 (4.92%)	
occurrences (all)	63	6	
Decreased appetite			
subjects affected / exposed	49 / 270 (18.15%)	5 / 122 (4.10%)	
occurrences (all)	55	6	
Hypomagnesaemia			
subjects affected / exposed	14 / 270 (5.19%)	5 / 122 (4.10%)	
occurrences (all)	17	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2016	Amendment 1: 1. Incorporated changes required by the voluntary harmonization procedure (VHP) assessment of the protocol after clinical trial application in Europe. VHP-required changes and sponsor changes were implemented to specify/clarify the schedule of events and laboratory tests, as well as to correct errors. 2. Acceptable contraceptive methods were specified. 3. Documented pregnancy was added as a discontinuation criterion. 4. Study center regions for subgroup analyses were specified to be North America, Europe, Asia-Pacific, and Other. 5. Additional trial termination criteria were added.
19 September 2017	Amendment 2: 1. Incorporated changes from minor UK/France amendment 1.1 2. Entry criteria, assessments, and procedural details were clarified to ensure study integrity. 3. Specifically, inclusion criterion #4 was modified to clarify that subjects were eligible if they were transfusion-dependent at screening, whether or not they were transfusion-dependent before HMA treatment and that disease progression could also happen after Cycle, as well as to more clearly align the disease progression definition for BM blasts and hemoglobin with the IWG 2006 progression criteria. 4. Clarified that blood samples were sufficient for gene mutation analysis. 5. Clarified that BM assessments to confirm eligibility may be collected within 28 days before randomisation (instead of 28 days before first dose) and cytogenetic assessments.
15 February 2018	Amendment 3: 1. Excluded subjects with a life expectancy of less than one month because these subjects would not have enough time for the study treatment to show an effect. 2. Allowed for primary analysis at or after 12 months of follow-up if 277 death events occurred (instead of 316 death events), to keep the study duration to a reasonable time, if fewer death events than anticipated have occurred, without significantly compromising the power of the study. 3. Allowed hydroxyurea in the first 30 days of guadecitabine treatment for subjects who had proliferative disease such as CMML, to control high White Blood Cells (WBC) counts and allow subjects to receive at least 2 cycles of treatment. 4. Clarified that, after discontinuing study treatment, subjects should not withdraw consent just because they wish to participate in another experimental study. 5. Clarified that survival status (at least) should be pursued, and a subject was still considered to be on study, even if a subject refused one or more longterm follow-up visits. This was to protect the study primary endpoint of overall survival. 6. Specified that conversion to AML was to be assessed, as this was an important milestone for disease progression. 7. Clarified that subjects assigned to BSC had Electrocardiography (ECG) assessment at the safety follow-up visit, as well as on Cycle 1 Day 1, consistent with the schedule of events. 8. Clarified and simplified the Pharmacokinetics PK analyses. 9. Clarified that a WBC differential manual count was to be conducted if there was suspicion of PB blasts.
02 October 2018	Amendment 4: 1. Excluded subjects with TP53 mutations: Based on emerging data, it was possible that, as a group, subjects with TP53 mutations were less likely to benefit from guadecitabine treatment. 2. Increased screening period from 14 to 21 days, to allow time for study centers to receive TP53 mutation results before randomisation. 3. Allowed institutional standard follow-up for subjects receiving TC: Subjects assigned to TC (LDAC, standard IC, or BSC) may have been followed up according to their investigative centers' standard practice, for convenience for both subject and study center. 4. Allowed a 4-day window for Day 1 weight assessment in each cycle: This corresponded to the 4-day window for hematology assessment and eliminated unnecessary repeat assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported