Clinical trial results:
A Phase 1/2, Dose and Schedule Finding Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Oral Azacitidine (CC-486) in Subjects with Acute Myeloid Leukemia or Myelodysplastic Syndromes after Allogeneic Hematopoietic Stem Cell Transplantation.

Summary

EudraCT number	2012-005805-36
Trial protocol	GB
Global end of trial date	26 May 2017

Results information

Result version number	v1 (current)
This version publication date	10 June 2018
First version publication date	10 June 2018

Trial information

Trial identification

Sponsor protocol code	CC-486-AML-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01835587
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Barry Skikne, MD, Celgene Corporation, 01 913-266-0334, BSkikne@Celgene.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	14 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the maximum tolerated dose (MTD) of oral azacitidine in subjects with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) after allogeneic hematopoietic stem cell transplantation (HSCT)

Protection of trial subjects:

Patient Confidentiality and Personal Data Protection. This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	30
EEA total number of subjects	2

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)	15
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The multicenter study was conducted in the United States and the United Kingdom. Participants were enrolled at 5 study sites.

Pre-assignment

Screening details:

Participants with a confirmed diagnosis of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who received an allogeneic hematopoietic stem cell transplant (HSCT) were eligible to participate and begin study drug between 42 and 84 days post HSCT. One participant was enrolled into the study but discontinued before being treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CC-486 200 mg Days 1-7 (Cohort 1)

Arm description:

Participants received CC-486 200 mg by mouth (PO) once daily (QD) on Days 1 to 7 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event (AE), disease recurrence or relapse, progressive disease (PD), development of Grade III/IV acute graft versus host disease (GVHD), withdrawal of consent, lost to follow-up, protocol violation or death.

Arm type	Experimental
Investigational medicinal product name	CC-486
Investigational medicinal product code	
Other name	Oral Azacitidine
Pharmaceutical forms	Coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

CC-486 200 mg on days 1-7 of each 28-day cycle.

Arm title	CC-486 300 mg Days 1-7 (Cohort 2)

Arm description:

Participants received CC-486 300 mg by mouth once daily on Days 1 to 7 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease, withdrawal of consent, lost to follow-up, protocol violation or death.

Arm type	Experimental
Investigational medicinal product name	CC-486
Investigational medicinal product code	
Other name	Oral Azacitidine
Pharmaceutical forms	Coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

CC-486 300 mg on days 1-7 of each 28-day cycle.

Arm title	CC-486 150 mg Days 1-14 (Cohort 3A)

Arm description:

Participants received CC-486 150 mg by mouth once daily on Days 1 to 14 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or

relapse, progressive disease, development of Grade III/IV acute graft versus host disease, withdrawal of consent, lost to follow-up, protocol violation or death.

Arm type	Experimental
Investigational medicinal product name	CC-486
Investigational medicinal product code	
Other name	Oral Azacitidine
Pharmaceutical forms	Coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

CC-486 150 mg on days 1-14 of each 28-day cycle.

Arm title	CC-486 200 mg Days 1-14 (Cohort 3)

Arm description:

Participants received CC-486 200 mg by mouth once daily on Days 1 to 14 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease (GVHD), withdrawal of consent, lost to follow-up, protocol violation or death.

Arm type	Experimental
Investigational medicinal product name	CC-486
Investigational medicinal product code	
Other name	Oral Azacitidine
Pharmaceutical forms	Coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

CC-486 200 mg on days 1-14 of each 28-day cycle.

Number of subjects in period 1	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)
Started	3	4	4
Completed	1	0	2
Not completed	2	4	2
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	2	-	-
Adverse event, non-fatal	-	-	2
Miscellaneous	-	1	-
Disease Recurrence or Relapse	-	3	-

Number of subjects in period 1	CC-486 200 mg Days 1-14 (Cohort 3)
Started	19
Completed	10
Not completed	9
Adverse event, serious fatal	1
Consent withdrawn by subject	3
Adverse event, non-fatal	2
Miscellaneous	-

Disease Recurrence or Relapse	3

Baseline characteristics

Reporting groups	
Reporting group title	CC-486 200 mg Days 1-7 (Cohort 1)
Reporting group description:	
Participants received CC-486 200 mg by mouth (PO) once daily (QD) on Days 1 to 7 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event (AE), disease recurrence or relapse, progressive disease (PD), development of Grade III/IV acute graft versus host disease (GVHD), withdrawal of consent, lost to follow-up, protocol violation or death.	
Reporting group title	CC-486 300 mg Days 1-7 (Cohort 2)
Reporting group description:	
Participants received CC-486 300 mg by mouth once daily on Days 1 to 7 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease, withdrawal of consent, lost to follow-up, protocol violation or death.	
Reporting group title	CC-486 150 mg Days 1-14 (Cohort 3A)
Reporting group description:	
Participants received CC-486 150 mg by mouth once daily on Days 1 to 14 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease, withdrawal of consent, lost to follow-up, protocol violation or death.	
Reporting group title	CC-486 200 mg Days 1-14 (Cohort 3)
Reporting group description:	
Participants received CC-486 200 mg by mouth once daily on Days 1 to 14 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease (GVHD), withdrawal of consent, lost to follow-up, protocol violation or death.	

Reporting group values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)
Number of subjects	3	4	4
Age categorical Units: Subjects			
Adults (18-64 years)	0	3	3
From 65-84 years	3	1	1
Age Continuous Units: Years			
arithmetic mean	68.3	47.8	61.8
standard deviation	± 5.77	± 18.26	± 8.73
Sex: Female, Male Units: Subjects			
Female	1	0	0
Male	2	4	4
Diagnosis at Study Entry			
Diagnosis of AML or MDS			
Units: Subjects			
Acute Myeloid Leukemia	2	4	4
Myelodysplastic Syndrome	1	0	0
AML World Health Organization (WHO) Classification			
AML is classified using the WHO classification system based upon a combination of morphology, immunophenotype, genetics, and clinical features. There are several broad groups and include: 1. AML with genetic abnormalities; 2. AML with multilineage dysplasia 3. AML related to previous chemotherapy			

or radiation 4. Unspecified AML - do not fall into the above groups			
Units: Subjects			
AML With Recurrent Genetic Abnormalities	0	2	0
AML With Myelodysplasia Related Changes	0	0	1
Therapy Related Myeloid Neoplasms	0	0	1
AML Not Otherwise Specified	2	2	2
Diagnosis of MDS	1	0	0
MDS International Prognostic Scoring System (IPSS) Risk Classification			
The MDS IPSS score assesses the severity of MDS based on 3 prognostic factors each assigned a score: the percentage of bone marrow blasts, chromosome changes in the marrow cells (karyotype) and the presence of one or more low blood cell counts (cytopenias). The IPSS score is the sum of the bone marrow blast + karyotype + cytopenia score and ranges from 0 (low risk) to 3.5 (high risk). Prognosis is categorized as Low risk (score = 0), Intermediate-1 (score 0.5 to 1.0), Intermediate-2 (score 1.5 to 2.0) or High risk (score ≥ 2.5).			
Units: Subjects			
INT-1	0	0	0
INT-2	1	0	0
High	0	0	0
Diagnosis of AML	2	4	4
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status is used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living activities of the subject and determine appropriate treatment and prognosis. 0 = Fully Active (Most Favorable Activity); 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, No self-care (Least Favorable Activity)			
Units: Subjects			
0 = Fully Active	1	1	1
1 = Restrictive but ambulatory	2	3	3
2 = Ambulatory but unable to work	0	0	0
Race			
Units: Subjects			
Asian	0	1	0
White	3	3	4
Not Collected or Reported	0	0	0
Time from MDS or AML Diagnosis to Allogeneic HSCT			
Units: months			
arithmetic mean	8.6	6.4	3.5
standard deviation	± 6.79	± 4.35	± 1.71

Reporting group values	CC-486 200 mg Days 1-14 (Cohort 3)	Total	
Number of subjects	19	30	
Age categorical			
Units: Subjects			
Adults (18-64 years)	9	15	
From 65-84 years	10	15	
Age Continuous			
Units: Years			
arithmetic mean	60.8		
standard deviation	± 12.60	-	

Sex: Female, Male Units: Subjects			
Female	4	5	
Male	15	25	
Diagnosis at Study Entry			
Diagnosis of AML or MDS			
Units: Subjects			
Acute Myeloid Leukemia	16	26	
Myelodysplastic Syndrome	3	4	
AML World Health Organization (WHO) Classification			
AML is classified using the WHO classification system based upon a combination of morphology, immunophenotype, genetics, and clinical features. There are several broad groups and include: 1. AML with genetic abnormalities; 2. AML with multilineage dysplasia 3. AML related to previous chemotherapy or radiation 4. Unspecified AML - do not fall into the above groups			
Units: Subjects			
AML With Recurrent Genetic Abnormalities	7	9	
AML With Myelodysplasia Related Changes	2	3	
Therapy Related Myeloid Neoplasms	0	1	
AML Not Otherwise Specified	7	13	
Diagnosis of MDS	3	4	
MDS International Prognostic Scoring System (IPSS) Risk Classification			
The MDS IPSS score assesses the severity of MDS based on 3 prognostic factors each assigned a score: the percentage of bone marrow blasts, chromosome changes in the marrow cells (karyotype) and the presence of one or more low blood cell counts (cytopenias). The IPSS score is the sum of the bone marrow blast + karyotype + cytopenia score and ranges from 0 (low risk) to 3.5 (high risk). Prognosis is categorized as Low risk (score = 0), Intermediate-1 (score 0.5 to 1.0), Intermediate-2 (score 1.5 to 2.0) or High risk (score ≥ 2.5).			
Units: Subjects			
INT-1	1	1	
INT-2	1	2	
High	1	1	
Diagnosis of AML	16	26	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status is used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living activities of the subject and determine appropriate treatment and prognosis. 0 = Fully Active (Most Favorable Activity); 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, No self-care (Least Favorable Activity)			
Units: Subjects			
0 = Fully Active	8	11	
1 = Restrictive but ambulatory	11	19	
2 = Ambulatory but unable to work	0	0	
Race Units: Subjects			
Asian	0	1	
White	18	28	
Not Collected or Reported	1	1	
Time from MDS or AML Diagnosis to Allogeneic HSCT Units: months			
arithmetic mean	10.6		
standard deviation	± 16.72	-	

End points

End points reporting groups

Reporting group title	CC-486 200 mg Days 1-7 (Cohort 1)

Reporting group description:

Participants received CC-486 200 mg by mouth (PO) once daily (QD) on Days 1 to 7 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event (AE), disease recurrence or relapse, progressive disease (PD), development of Grade III/IV acute graft versus host disease (GVHD), withdrawal of consent, lost to follow-up, protocol violation or death.

Reporting group title	CC-486 300 mg Days 1-7 (Cohort 2)

Reporting group description:

Participants received CC-486 300 mg by mouth once daily on Days 1 to 7 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease, withdrawal of consent, lost to follow-up, protocol violation or death.

Reporting group title	CC-486 150 mg Days 1-14 (Cohort 3A)

Reporting group description:

Participants received CC-486 150 mg by mouth once daily on Days 1 to 14 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease, withdrawal of consent, lost to follow-up, protocol violation or death.

Reporting group title	CC-486 200 mg Days 1-14 (Cohort 3)

Reporting group description:

Participants received CC-486 200 mg by mouth once daily on Days 1 to 14 of each 28-day cycle for a maximum duration of 12 months or until they experienced an adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease (GVHD), withdrawal of consent, lost to follow-up, protocol violation or death.

Subject analysis set title	CC-486 200 mg Days 1-7 and Days 1-14
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pharmacokinetic (PK) data from participants who received CC-486 200 mg by mouth daily were combined because the wash-out period between
the PK sample collection and previous CC-486 dose was greater than 7-fold the half-life elimination of the drug, and CC 486 does not accumulate following multiple administrations.

Subject analysis set title	CC-486 300 mg Days 1-7
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PK data for participants who received CC-486 300 mg by mouth once daily on Days 1 to 7 of each 28 day cycle for a maximum duration of 12 months or until they experienced, adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease, withdrawal of consent, lost to follow-up, protocol violation or death.

Subject analysis set title	CC-486 150 mg Days 1-14
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD data for participants who received CC-486 150 mg by mouth once daily on Days 1 to 14 of each 28-day cycle for a maximum duration of 12 months or until they experienced, adverse event, disease recurrence or relapse, progressive disease, development of Grade III/IV acute graft versus host disease, withdrawal of consent, lost to follow-up, protocol violation or death.

Primary: The Number of Dose Limiting Toxicities (DLT)

End point title	The Number of Dose Limiting Toxicities (DLT)[1]

End point description:

A DLT included events that started within 28 days of the first dose of CC-486 in a 28-day cycle, constituted a change from baseline irrespective of outcome, as decided by the investigator to be related to CC-486 including:
• ≥ Grade (GR) 3 nausea, diarrhea, or vomiting despite the use of medical support
• Other significant nonhematologic toxicity of ≥ GR 3 considered not related to the disease or intercurrent illness

• Absolute neutrophil count (ANC) < 0.5 x 10^9/L for > 1 week despite growth factor support
• Platelets < 25 x 10^9/L for > 1 week despite transfusion support
• Failure of recovery to an ANC ≥ 1.0 x 10^9/L and/or platelets ≥ 50 x 10^9/L with a hypocellular marrow by 56 days after the start of a cycle of CC-486 not due to relapse or progressive disease.
The maximum tolerated dose is defined as the cohort delivering the highest dose in which no more than 33% of the evaluable subjects had a DLT The safety population included subjects who received ≥ 1 dose of CC-486

End point type	Primary

End point timeframe:

2 months (Cycles 1 and 2)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint of finding the maximum tolerated dose did not require statistical analysis be conducted.

End point values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)	CC-486 200 mg Days 1-14 (Cohort 3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	4	19
Units: Participants	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAE)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAE)

End point description:

A TEAE was defined as any AE with an onset date on or after the first dose of IP or any event already present that worsened in severity or increased in frequency after exposure to IP up to 28 days after the last dose. In addition, an AE that occurred beyond the timeframe and was assessed by the doctor as possibly related to IP was considered to be treatment-emergent. Severity was assessed using National Cancer Institute Common Toxicity Terminology Criteria for AEs (NCI CTCAE) version 4.0, where 1= Mild; 2= Moderate; 3= Severe; 4= Life-threatening; 5= Death related to AE. Serious AEs resulted in death, were life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, congenital anomaly, or resulted in a medical event that may have jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes above. The safety population includes subjects who received at least one dose of CC-486.

End point type	Secondary

End point timeframe:

From the first dose of IP up to 28 days after the last dose of IP. The median duration of exposure was 252.5 days overall; up to the final data cut-off date of 14 July 2017.

End point values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)	CC-486 200 mg Days 1-14 (Cohort 3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	4	19
Units: participants				
Any TEAE	3	4	4	19

Any TEAE With A Grade 3 or 4	2	3	3	14
Any TEAE Related to IP	3	3	4	17
TEAE With A Grade 3 or 4 Related to IP	1	1	3	8
Serious TEAE	1	3	2	6
Serious TEAE Related to IP	1	0	1	2
TEAE With Outcome of Death	0	0	0	1
TEAE Leading to Discontinuation of IP	0	0	2	6
TEAE Related to IP and Leading to Stopping IP	0	0	1	3
TEAE Leading to Dose Reduction	0	0	0	1
TEAE Leading to Dose Interruption	1	0	1	6
TEAE Leading to Dose Drug Interruption/Reduction	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Time to Discontinuation from Treatment

End point title	Kaplan Meier Estimate of Time to Discontinuation from Treatment

End point description:

The time to discontinuation from treatment was assessed as an estimate of treatment tolerability and was defined as the interval from the date of the first IP dose to the date of discontinuation from IP as indicated on the discontinuation from treatment case report form (CRF) page. Time to discontinuation from study treatment was analyzed using the Kaplan-Meier method where participants who did not discontinue were censored at the date of last visit. The safety population includes subjects who received at least one dose of CC-486.

End point type	Secondary

End point timeframe:

From the time of randomization until the end of treatment; the median duration of exposure was 252.5 days overall.

End point values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)	CC-486 200 mg Days 1-14 (Cohort 3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[2]	4[3]	4[4]	19[5]
Units: days				
number (not applicable)				
25th Percentile	184.0	104.5	228.5	58.0
Median	189.0	177.0	99999	389.0
75th Percentile	99999	189.0	99999	99999

Notes:

[2] - 99999= indicates time was not reached due to subjects remaining in study until study closure.

[3] - 99999= indicates time was not reached due to subjects remaining in study until study closure.

[4] - 99999= indicates time was not reached due to subjects remaining in study until study closure.

[5] - 99999= indicates time was not reached due to subjects remaining in study until study closure.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Graft Versus Host Disease During the Entire Course of the Study

End point title	Percentage of Participants With Graft Versus Host Disease During the Entire Course of the Study

End point description:

Acute graft versus host disease generally occurs after allogeneic hematopoietic stem cell transplantation. It is a reaction of donor immune cells against host tissues. The 3 main tissues that acute GVHD affects are the skin, liver, and gastrointestinal tract. Chronic GVHD is scored per the National Institute of Health consensus conference grading system. Clinical manifestations of chronic GVHD include skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma; dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract; and a rising serum bilirubin concentration. The safety population includes subjects who received at least one dose of CC-486.

End point type	Secondary

End point timeframe:

From the first dose of CC-486 up to study discontinuation or death. Up to final data cut off date of 14 July 2017; up to 186 weeks and 4 days

End point values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)	CC-486 200 mg Days 1-14 (Cohort 3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	4	19
Units: percentage of participants				
number (confidence interval 95%)	66.7 (9.43 to 99.16)	0.0 (0.00 to 60.24)	75.0 (19.41 to 99.37)	63.2 (38.36 to 83.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve from Time 0 to the Time of the Last Quantifiable Concentration Of CC-486 (AUC-t).

End point title	Area Under the Plasma Concentration-time Curve from Time 0 to the Time of the Last Quantifiable Concentration Of CC-486 (AUC-t).

End point description:

Area under the plasma concentration-time curve from Time 0 to the time of the last quantifiable concentration, calculated by linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing. The pharmacokinetic population included subjects with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

On Day 1 of Cycles 1 and 2 stay until 6 hours after CC-486 administration.

End point values	CC-486 200 mg Days 1-7 and Days 1-14	CC-486 300 mg Days 1-7	CC-486 150 mg Days 1-14	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[6]	5[7]	2[8]	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Without Concomitant Meds|	204.6 (± 63.0)	253.3 (± 26.6)	99999 (± 99999)	
With Concomitant Meds|	176.8 (± 69.0)	226.7 (± 54.5)	187.2 (± 34.1)	

Notes:

[6] - 4 Without Concomitant Meds
N = 20 With Concomitant Meds

[7] - N = 2 Without Concomitant Meds
N = 5 With Concomitant Meds

[8] - N = 0 Without Concomitant Meds;
99999= not applicable due to 0 subjects
N = 2 With Concomitant Me

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve from Time 0 to Extrapolated to Infinity (AUC-inf AUC0-∞) Of CC-486

End point title	Area Under the Plasma Concentration-Time Curve from Time 0 to Extrapolated to Infinity (AUC-inf AUC0-∞) Of CC-486

End point description:

Area under the plasma concentration-time curve from Time 0 extrapolated to infinity, calculated as [AUCt + Ct/ λz]. Ct is the last quantifiable concentration. No AUC extrapolation was performed with unreliable λz. If AUC %Extrap was ≥25%, AUC inf was not reported. The pharmacokinetic population included subjects with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

On Day 1 of Cycles 1 and 2 stay until 6 hours after the CC-486 administration

End point values	CC-486 200 mg Days 1-7 and Days 1-14	CC-486 300 mg Days 1-7	CC-486 150 mg Days 1-14	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[9]	5[10]	2[11]	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Without Concomitant Meds	206.0 (± 62.8)	218.4 (± 99999)	99999 (± 99999)	
With Concomitant Meds	187.5 (± 70.1)	232.5 (± 51.7)	188.6 (± 33.5)	

Notes:

[9] - N = 4 Without Concomitant Meds
N = 18 With Concomitant Meds

[10] - N= 1 Without Concomitant Meds
N= 5 With Concomitant Meds
99999=sample size could not be calculated

[11] - N = 0 Without Concomitant Meds
N = 2 With Concomitant Meds
99999= not applicable due to 0 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) Of CC-486

End point title	Maximum Observed Concentration (Cmax) Of CC-486

End point description:

Maximum observed plasma concentration, obtained directly from the observed concentration versus time data. The pharmacokinetic population included subjects with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

On Day 1 of Cycles 1 and 2 stay until 6 hours after oral azacitidine administration

End point values	CC-486 200 mg Days 1-7 and Days 1-14	CC-486 300 mg Days 1-7	CC-486 150 mg Days 1-14	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[12]	5[13]	2[14]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Without Concomitant Meds	151.9 (± 43.5)	149.8 (± 7.6)	99999 (± 99999)	
With Concomitant Meds	114.3 (± 73.4)	137.8 (± 65.7)	91.49 (± 25.1)	

Notes:

[12] - N = 4 Without Concomitant Meds
N = 20 With Concomitant Meds
[13] - N = 2 Without Concomitant Meds
N = 5 With Concomitant Meds
[14] - N = 0 Without Concomitant Meds
N = 2 With Concomitant Meds
99999= not applicable due to 0 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Concentration (Tmax) of CC-486

End point title	Time to Reach Maximum Concentration (Tmax) of CC-486

End point description:

Time to Cmax, obtained directly from the observed concentration versus time data. The pharmacokinetic population included subjects with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

On Day 1 of Cycles 1 and 2 stay until 6 hours after oral CC-486 administration

End point values	CC-486 200 mg Days 1-7 and Days 1-14	CC-486 300 mg Days 1-7	CC-486 150 mg Days 1-14	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[15]	5[16]	2[17]	
Units: hours				
median (full range (min-max))				
Without Concomitant Meds	0.77 (0.50 to 1.5)	2.3 (1.5 to 3.1)	99999 (99999 to 99999)	
With Concomitant Meds	144 (24.3 to 252)	2.0 (1.5 to 2.5)	2.0 (2.0 to 2.0)	

Notes:

[15] - N = 4 Without Concomitant Meds
N = 20 With Concomitant Meds
[16] - 2 Without Concomitant Meds
N = 5 With Concomitant Meds
[17] - N = 0 Without Concomitant Meds
N = 2 With Concomitant Meds
99999= not applicable due to 0 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-Life (T1/2) of CC-486

End point title	Terminal Half-Life (T1/2) of CC-486

End point description:

Terminal phase half-life in plasma, calculated as [(ln 2)/λz]. t1/2 was only calculated when a reliable estimate for λz could be obtained. The pharmacokinetic population included subjects with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

On Day 1 of Cycles 1 and 2 stay until 6 hours after oral CC-486 administration

End point values	CC-486 200 mg Days 1-7 and Days 1-14	CC-486 300 mg Days 1-7	CC-486 150 mg Days 1-14	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[18]	5[19]	2[20]	
Units: hours				
geometric mean (geometric coefficient of variation)				
Without Concomitant Meds	0.528 (± 6.8)	0.575 (± 99999)	99999 (± 99999)	
With Concomitant Meds	0.553 (± 24.5)	0.565 (± 44.3)	0.446 (± 20.6)	

Notes:

[18] - N = 4 Without Concomitant Meds
N = 18 With Concomitant Meds
[19] - N = 1 Without Concomitant Meds

N = 5 With Concomitant Meds
99999-sample size to small to calculate
[20] - N = 0 Without Concomitant Meds
N = 2 With Concomitant Meds
99999= not applicable due to 0 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Clearance (CL/F) of CC-486

End point title	Apparent Total Clearance (CL/F) of CC-486

End point description:

Apparent total clearance, calculated as [Dose/AUCinf]. The pharmacokinetic population included subjects with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

On Day 1 of Cycles 1 and 2 stay until 6 hours after oral CC-486 administration

End point values	CC-486 200 mg Days 1-7 and Days 1-14	CC-486 300 mg Days 1-7	CC-486 150 mg Days 1-14	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[21]	5[22]	2[23]	
Units: L/h				
geometric mean (geometric coefficient of variation)				
Without Concomitant Meds	971.1 (± 62.8)	1374 (± 99999)	99999 (± 99999)	
With Concomitant Meds	1067 (± 70.1)	1290 (± 51.7)	795.4 (± 33.5)	

Notes:

[21] - N = 4 Without Concomitant Meds
N = 18 With Concomitant Meds
[22] - N = 1 Without Concomitant Meds
N = 5 With Concomitant Meds
[23] - N = 0 Without Concomitant Meds
N = 2 With Concomitant Meds
99999= not applicable due to 0 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F) of CC-486

End point title	Apparent Volume of Distribution (Vz/F) of CC-486

End point description:

Apparent volume of distribution, calculated as [(CL/F)/λz].Apparent volume of distribution, calculated as [(CL/F)/λz]. The pharmacokinetic population included subjects with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

On Day 1 of Cycles 1 and 2 stay until 6 hours after oral CC-486 administration

End point values	CC-486 200 mg Days 1-7 and Days 1-14	CC-486 300 mg Days 1-7	CC-486 150 mg Days 1-14	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[24]	5[25]	2[26]	
Units: Liters				
geometric mean (geometric coefficient of variation)				
Without Concomitant Meds	739.9 (± 58.7)	1139 (± 99999)	99999 (± 99999)	
With Concomitant Meds	851.3 (± 77.6)	1052 (± 100.0)	511.8 (± 12.3)	

Notes:

[24] - N = 4 Without Concomitant Meds
N = 18 With Concomitant Meds
[25] - N = 1 Without Concomitant Meds
N = 5 With Concomitant Meds
99999-sample size to small to calculate
[26] - N = 0 Without Concomitant Meds
N =2 With Concomitant Meds
99999= not applicable due to 0 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Relapse or Progression

End point title	Percentage of Participants With Disease Relapse or Progression

End point description:

Disease relapse was defined as the reappearance of > 5% blasts in the bone marrow that persisted for at least 4 weeks. Disease progression was defined as the reappearance of > 10% of blasts in the bone marrow that persisted for at least 4 weeks. The preliminary efficacy population included all subjects who received at least one dose of IP and had at least one post-baseline efficacy assessment performed.

End point type	Secondary

End point timeframe:

Date of first dose of IP to disease relapse or progression; up to data cut-off date of 14 July 2017.

End point values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)	CC-486 200 mg Days 1-14 (Cohort 3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	4	19
Units: Percentage of Participants				
number (not applicable)	33.3	75.0	0	15.8

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Recurrence/Progression

End point title	Time to Disease Recurrence/Progression

End point description:

Time to disease relapse/progression was defined as the interval from the date of allogeneic HSCT to the date of treatment discontinuation or study discontinuation where reason for discontinuation is disease relapse or disease progression, or the date of disease progression recorded on the survival electronic Case Report Form page, whichever occurred first. Time to disease relapse/progression was analyzed using competing risk methods where death without documented relapse/progression was treated as a competing risk for relapse/progression. relapse/progression. The preliminary efficacy population included all subjects who received at least one dose of IP and had at least one post-baseline efficacy assessment performed.

End point type	Secondary

End point timeframe:

Date of allogenic HSCT to disease progression or discontinuation. Median number of days from first dose to disease relapse or progression was 963.0 days for Cohort 1, 743.5 days for Cohort 2, 657.5 days for Cohort 3A and 559.0 days for Cohort 3.

End point values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)	CC-486 200 mg Days 1-14 (Cohort 3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	4	19
Units: days				
arithmetic mean (standard deviation)	691.7 (± 436.10)	452.5 (± 493.50)	660.8 (± 218.12)	521.7 (± 310.53)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival was defined as the time from the date of allogeneic hematopoietic stem cell transplantation to death from any cause. The preliminary efficacy population included all subjects who received at least one dose of IP and had at least one post-baseline efficacy assessment performed.

End point type	Secondary

End point timeframe:

Date of the allogeneic HSCT to death from any cause. Median number of days participants were assessed from first dose to last contact was 963.0 days for Cohort 1, 743.5 days for Cohort 2, 675.5 days for Cohort 3A and 559.0 days for Cohort 3

End point values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)	CC-486 200 mg Days 1-14 (Cohort 3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[27]	4[28]	4[29]	19[30]
Units: Days				
number (not applicable)				
25th Percentile	741.0	304	99999	547
Median	99999	99999	99999	99999
75th Percentile	99999	99999	99999	99999

Notes:

[27] - 99999=median OS not reached due to long survival of subjects relative to study duration

[28] - 99999=median OS not reached due to long survival of subjects relative to study duration

[29] - 99999=median OS not reached due to long survival of subjects relative to study duration

[30] - 99999=median OS not reached due to long survival of subjects relative to study duration

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Relapse-Free Survival (RFS)

End point title	Kaplan Meier Estimate of Relapse-Free Survival (RFS)

End point description:

Relapse-free survival was defined as the interval from the date of allogeneic HSCT to the date of first documented > 5% blasts in the bone marrow or death from any cause, whichever occurred first. Participants who were still alive and continued to have less than or equal to 5% blasts in the bone marrow or who were lost to follow-up were censored at the date of their last response assessment. The preliminary efficacy population included all subjects who received at least one dose of IP and had at least one post-baseline efficacy assessment performed.

End point type	Secondary

End point timeframe:

Date of allogeneic HSCT to date of progression or death from any cause; median number of days subjects were assessed from first dose to last contact was 963.0 days for Cohort 1, 743.5 days for Cohort 2, 675.5 days for Cohort 3A and 559.0 days for Cohort 3

End point values	CC-486 200 mg Days 1-7 (Cohort 1)	CC-486 300 mg Days 1-7 (Cohort 2)	CC-486 150 mg Days 1-14 (Cohort 3A)	CC-486 200 mg Days 1-14 (Cohort 3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4[31]	4[32]	19[33]
Units: Days				
25th Percentile	741	183	99999	397
Median	921	255	99999	99999
75th Percentile	1101	99999	99999	99999

Notes:

[31] - 99999=median PFS not reached due to long progression free in subjects relative to study duration.

[32] - 99999=median PFS not reached due to long progression free in subjects relative to study duration.

[33] - 99999=median PFS not reached due to long progression free in subjects relative to study duration.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of IP up to 28 days after the last dose of IP. The median duration of exposure was 252.5 days overall.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	200 mg x 7 days
Reporting group description: -	
Reporting group title	300 mg x 7 days
Reporting group description: -	
Reporting group title	150mg x 14 days
Reporting group description: -	
Reporting group title	200 mg x 14 days

Reporting group description: -

Serious adverse events	200 mg x 7 days	300 mg x 7 days	150mg x 14 days
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	3 / 4 (75.00%)	2 / 4 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	200 mg x 14 days		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	200 mg x 7 days	300 mg x 7 days	150mg x 14 days
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Basal cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Hypotension			

subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	2	3	4
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Chronic graft versus host disease in skin			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Graft versus host disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Graft versus host disease in gastrointestinal tract			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Graft versus host disease in liver			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Graft versus host disease in skin			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Obliterative bronchiolitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Anxiety			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	3
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	0	0	6
Blood potassium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	0	0	5
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Dysgeusia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Headache			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Radial nerve palsy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 4 (75.00%)	3 / 4 (75.00%)
occurrences (all)	2	3	5
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	0	0	3
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	0	0	5
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Thrombocytopenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	1	1	2

Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Keratitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Photophobia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Retinal detachment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	5	4	3
Dry mouth			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	4 / 4 (100.00%)
occurrences (all)	7	3	6
Oesophagitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	3	1	2
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Dry skin			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Rosacea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Bladder spasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Chronic kidney disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0

Arthritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Joint range of motion decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Rotator cuff syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Catheter site cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Corneal infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nail infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pneumonia respiratory syncytial viral			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin candida			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	3	4	0
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Diabetes mellitus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	4
Hyperuricaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	0	0	3

Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	6
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	3 / 4 (75.00%)
occurrences (all)	0	0	5
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	3
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	3
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Vitamin D deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	200 mg x 14 days		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Basal cell carcinoma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Haematoma			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Hypotension			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Orthostatic hypotension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	8		
Non-cardiac chest pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Immune system disorders			

Chronic graft versus host disease in skin				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Graft versus host disease				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Graft versus host disease in gastrointestinal tract				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Graft versus host disease in liver				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Graft versus host disease in skin				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	3			
Dyspnoea				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Nasal congestion				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Obliterative bronchiolitis				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	2			
Rhinitis allergic				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences (all)	3			
Sneezing				
subjects affected / exposed	0 / 19 (0.00%)			
occurrences (all)	0			
Upper-airway cough syndrome				

subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Blood creatinine increased			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
Blood potassium decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 5		
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Weight decreased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Fall subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Post-traumatic pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Skin abrasion subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Radial nerve palsy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	12		
Leukopenia			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	7		
Lymphopenia			

subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	7		
Neutropenia			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	6		
Thrombocytopenia			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	10		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Keratitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Photophobia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Retinal detachment			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	6		
Constipation			

subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	11 / 19 (57.89%)		
occurrences (all)	16		
Dry mouth			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Gastrointestinal pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	12 / 19 (63.16%)		
occurrences (all)	16		
Oesophagitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	13		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Pruritus			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Rash erythematous			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Rosacea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Bladder spasm			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Chronic kidney disease			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Arthritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Joint range of motion decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Osteopenia			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain in jaw			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rotator cuff syndrome			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Catheter site cellulitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Clostridium difficile colitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Clostridium difficile infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Corneal infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Nail infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Skin candida			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Diabetes mellitus			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gout			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	6		
Hyperkalaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Vitamin D deficiency			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2015	• Hematologic toxicities that did not meet the definition of DLT were observed early in Cohort 3 (200 mg QD for 14 days), which prompted the following changes: - Incorporation of an alternative cohort with azacitidine total exposure lower than Cohort 3, specifically 150 mg QD for 14 days - Increase in the minimal platelet count required for study entry from 25 x 10^9/L to 75 x 10^9/L - Removal of the 21-day treatment schedules - Increase in the lower limit for platelet count in the definition of DLT - Change to the neutropenia and thrombocytopenia criteria for interrupting or resuming IP • Other changes included the following: - Cohort 1 (200 mg QD for 7 days) was safe and well tolerated without DLT. Therefore, lower dose cohorts (100 mg QD for Days 1 to 7 and 150 mg QD for Days 1 to 7) were removed. - Pregnancy testing was added on Cycle 5 Day 1 and beyond. A change was also made to require serum pregnancy test at screening, instead of a serum or urine pregnancy test. - The reference section was updated. - New protocol template language related to safety and the end of study definition was added. - Minor typographical corrections were made. - Which subjects should undergo standard PK sampling and sparse PK sampling was clarified. - The timing for bone marrow aspirate or biopsy during screening was clarified. - The definition of overdose added and AE reporting procedures for overdose were clarified to conform to template updates. - The stepwise reduction of dose or treatment duration was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported