Clinical trial results:
A randomized, multicenter, open-label, Phase 2 study with a safety run-in part to evaluate safety, pharmacodynamics and efficacy of azacitidine compared to no anticancer treatment in children and young adults with acute myeloid leukemia in molecular relapse after first complete remission

Summary

EudraCT number	2014-002172-92
Trial protocol	DE DK NL FR
Global end of trial date	08 October 2019

Results information

Result version number	v1 (current)
This version publication date	17 April 2020
First version publication date	17 April 2020

Trial information

Trial identification

Sponsor protocol code	AZA-AML-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02450877
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, 01 908-673-9100, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Bouchra Benettaib, Celgene Corporation, 01 908 673 9194, BBenettaib@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Safety Run-in Part
To establish a safe and tolerable dose of azacitidine to be used in the randomized part of the study.

Randomized Part
To evaluate the effect of azacitidine treatment in acute myeloid leukemia (AML) subjects at molecular relapse after complete response (CR1) when compared to no treatment with regard to the progression-free rate (PFR) at Day 84 (±4 days) post randomization.

Protection of trial subjects:

Patient Confidentiality, Informed Consent, Archiving of Essential Documents,

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Netherlands: 2
Worldwide total number of subjects	7
EEA total number of subjects	7

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)	6

Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Seven children were enrolled from 3 centers located in Denmark, Germany and the Netherlands.

Pre-assignment

Screening details:

The Randomized Part of the study was not conducted. The study was transitioned to a single-arm study (N=20) Phase 2 non-Celgene sponsored study.

Period 1

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

Arms

Arm title	Azacitidine

Arm description:

Participants received azacitidine 100 mg/m^2 by intravenous administration on days 1 to 7 of each 28-day treatment cycle for a maximum of 3 cycles.

Arm type	Experimental
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	Vidaza
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Azacitidine 100 mg/m^2 by IV administration on days 1 to 7 of each 28 day treatment cycle.

Number of subjects in period 1	Azacitidine
Started	7
Completed	5
Not completed	2
Disease Relapse	1
Death	1

Baseline characteristics

Reporting groups	
Reporting group title	Azacitidine
Reporting group description:	
Participants received azacitidine 100 mg/m^2 by intravenous administration on days 1 to 7 of each 28-day treatment cycle for a maximum of 3 cycles.	

Reporting group values	Azacitidine	Total	
Number of subjects	7	7	
Age Categorical Units: Subjects			
Children (2-11 years)	6	6	
Adolescents (12-17 years)	1	1	
Age Continuous Units: years			
median	6.7		
full range (min-max)	2 to 12	-	
Gender Categorical Units: Subjects			
Female	2	2	
Male	5	5	
Race Units: Subjects			
White	7	7	
Ethnicity Units: Subjects			
Not Hispanic or Latino	7	7	
World Health Organization Acute Myeloid Leukemia Classification			
Eligible subjects must have had a documented diagnosis of AML with at least one of the following molecular aberrations t(8;21), RUNX1-RUNX1T1, inv(16), CBFb/MYH11, t(9;11), MLL-AF9, NPM1 mutation, or FLT3-ITD mutation. A subject was counted more than once if there was several AML diagnoses. t(8;21), RUNX1-RUNX1T1 = 3 inv(16), CBFb/MYH11 = 4 FLT3-ITD mutation = 1			
Units: Subjects			
t(8;21), RUNX1-RUNX1T1	3	3	
inv(16), CBFb/MYH11	4	4	
Duration of the Disease Units: Months			
median	10.320		
full range (min-max)	9.00 to 13.11	-	

End points

End points reporting groups

Reporting group title	Azacitidine

Reporting group description:

Participants received azacitidine 100 mg/m^2 by intravenous administration on days 1 to 7 of each 28-day treatment cycle for a maximum of 3 cycles.

Primary: Part 1 Safety Run In: Number of Participants with Dose Limiting Toxicities (DLT)

End point title	Part 1 Safety Run In: Number of Participants with Dose Limiting Toxicities (DLT)[1]

End point description:

Dose limiting toxicities were evaluated during the Part 1 Safety Run-in period in the first 6 subjects during Cycle 1. The severity grading was determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. A DLT is defined as below:
Hematologic DLT:
• Grade 3 or 4 hematologic toxicity requiring treatment delay > 21 days
(disease-related Grade 3 or 4 hematologic toxicity was not counted as a DLT)

Non-Hematologic DLT:
• Grade 4 nonhematologic toxicity (excluding transient transaminase elevation)
• Grade 3 nonhematological toxicity lasting more than 7 days despite optimal treatment with standard supportive measures

• Grade 5 Adverse Events (AEs) considered related to study treatment
The safety population was defined as all subjects who received at least 1 dose of study therapy if assigned to receive azacitidine.

End point type	Primary

End point timeframe:

Cycle 1 (28 days)

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: No statistical analysis was performed.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAE)[2]

End point description:

Treatment emergent adverse events were defined as any AEs occurring or worsening on or after the first treatment of the study medication and up to and including 28 days after the last dose. The intensity of

AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.0, May 2009). For all other AEs not described in the NCI-CTCAE criteria, the intensity was assessed by the investigator as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or death (grade 5). The safety population was defined as all subjects who received at least 1 dose of study therapy if assigned to receive azacitidine.

End point type	Primary

End point timeframe:

From the first dose of investigational product (IP) up to and including 28 day after the last dose of azacitidine; up to 01 November 2019; median treatment duration was 12.00 weeks, with minimum and maximum durations of 8.0 and 13.9 weeks, respectively.

Notes:

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

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
≥1 TEAE	7			
≥1 Grade 3 or Higher TEAE	7			
≥1 Treatment-related TEAE	7			
≥1 Treatment-related Grade 3 or Higher TEAE	5			
≥1 Serious TEAE	3			
≥1 Treatment-related Serious TEAE	1			
≥1 TEAE Leading to Death	0			
≥1 TEAE Leading to IP Discontinuation	0			
≥1 TEAE Leading to IP Dose Reduction	0			
≥1 TEAE Leading to IP Dose Interruption	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a Molecular Response [by Minimal Residual Disease (MRD)] at Day 84

End point title	Number of Participants with a Molecular Response [by Minimal Residual Disease (MRD)] at Day 84

End point description:

The number of participants with a molecular response was defined as the number of subjects with molecular response [1 log or more decrease in defined MRD molecular markers from baseline for all subject-specific genes or aberrations in peripheral blood (PB) samples and bone marrow (BM) aspirates]. The ITT population included participants who were enrolled in the study regardless of whether or not they received any of the study treatment.

End point type	Secondary

End point timeframe:

Date of Enrollment to Day 84

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Azacitidine

End point title	Maximum Plasma Concentration (Cmax) of Azacitidine

End point description:

Cmax was defined as the observed maximum plasma concentration, obtained directly from the observed concentration versus time. The pharmacokinetic (PK) population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at Cycle 1 Day 5 and 6 (C1 D5,D6) and post dose at Cycle 1 Day 7 (C1D7) at 5 min, 0.5 hours, 1, 4, and 6 hours; subjects > 20 kg, pre-dosing at C1 D5,D6 and D7, post dose on C1D7 at 5 min, 0.5 hours, 1, 2, 4, 6 hours.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1556.633 (± 201.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma Concentration (Tmax) of Azacitidine

End point title	Time to Maximum Plasma Concentration (Tmax) of Azacitidine

End point description:

Tmax was defined as the observed time to maximum plasma concentration of azacitidine. The pharmacokinetic population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at C1 D5, D6 and post dose at C1 D7 at 5 min, 0.5 hours, 1, 4, and 6 hours; subjects > 20 kg, pre-dosing at C1 D5, D6 and D7, post dose on C1 D7 at 5 min, 0.5 hours, 1, 2, 4, 6 hours.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Hours				
median (full range (min-max))	0.090 (0.08 to 0.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve from Time 0 to the Last Quantifiable Concentration (AUC0-t) of Azacitidine

End point title	Area Under the Plasma Concentration Versus Time Curve from Time 0 to the Last Quantifiable Concentration (AUC0-t) of Azacitidine

End point description:

AUC0-t was defined as the area under the plasma concentration-time curve from time zero to the last quantifiable time point, for azacitidine, calculated by the linear trapezoidal rule. The pharmacokinetic population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at C1 D5, D6 and post dose at C1 D7 at 5 min, 0.5 hours, 1, 4, and 6 hours; subjects > 20 kg, pre-dosing at C1 D5, D6 and D7, post dose on C1 D7 at 5 min, 0.5 hours, 1, 2, 4, 6 hours.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	885.652 (± 86.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve from Time 0 to 24 Hours Post-dose (AUC0-24) of Azacitidine

End point title	Area Under the Plasma Concentration-time Curve from Time 0 to 24 Hours Post-dose (AUC0-24) of Azacitidine

End point description:

Area under the plasma concentration-time curve from time 0 to 24 hours post- dose of azacitidine following multiple doses of azacitidine. The pharmacokinetic population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at C1 D5, D6 and post dose at C1 D7 at 5 min, 0.5 hours, 1, 4, and 6 hours; subjects > 20 kg, pre-dosing at C1 D5, D6 and D7, post dose on C1 D7 at 5 min, 0.5 hours, 1, 2, 4, 6 hours.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	899.647 (± 87.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve from Time Zero 0 Infinity (AUC∞) of Azacitidine

End point title	Area Under the Plasma Concentration-time Curve from Time Zero 0 Infinity (AUC∞) of Azacitidine

End point description:

Area under the plasma concentration-time curve from time zero to infinity, extrapolated to infinity, calculated by the linear trapezoidal rule and extrapolated to infinity and was calculated according to the following equation: AUC∞ = AUCt + (Ct/λz), where Ct is the last quantifiable concentration. No AUC extrapolation was performed with unreliable λz. If AUC% Ext was > 25%, AUC∞ was not be reported. The pharmacokinetic population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at C1 D5, D6 and post dose at C1 D7 at 5 min, 0.5 hours, 1, 4, and 6 hou

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	787.616 (± 88.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Phase Rate Constant (λz) of Azacitdine

End point title	Terminal Phase Rate Constant (λz) of Azacitdine

End point description:

Terminal phase rate constant, determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. The pharmacokinetic population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at C1 D5, D6 and post dose at C1 D7 at 5 min, 0.5 hours, 1, 4, and 6 hours; subjects > 20 kg, pre-dosing at C1 D5, D6 and D7, post dose on C1 D7 at 5 min, 0.5 hours, 1, 2, 4, 6 hours.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: L/hr				
geometric mean (geometric coefficient of variation)	1.489 (± 59.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Phase Half-life (t½) of Azacitidine

End point title	Terminal Phase Half-life (t½) of Azacitidine

End point description:

Terminal phase half-life was calculated according to the following equation: t½ = 0.693/λz. The pharmacokinetic population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at C1 D5, D6 and post dose at C1 D7 at 5 min, 0.5 hours, 1, 4, and 6 hours; subjects > 20 kg, pre-dosing at C1 D5, D6 and D7, post dose on C1 D7 at 5 min, 0.5 hours, 1, 2, 4, 6 hours.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Hours				
geometric mean (geometric coefficient of variation)	0.380 (± 32.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Plasma Clearance (CL/) of Azacitidine

End point title	Apparent Total Plasma Clearance (CL/) of Azacitidine

End point description:

Apparent total clearance was calculated as Dose/AUC∞. The pharmacokinetic population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at C1 D5, D6 and post dose at C1 D7 at 5 min, 0.5 hours, 1, 4, and 6 hours; subjects > 20 kg, pre-dosing at C1 D5, D6 and D7, post dose on C1 D7 at 5 min, 0.5 hours, 1, 2, 4, 6 hours.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: mL/hr				
geometric mean (geometric coefficient of variation)	127199.754 (± 73.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F) of Azacitidine

End point title	Apparent Volume of Distribution (Vz/F) of Azacitidine

End point description:

Apparent volume of distribution of azacitidine was calculated according to the equation Vz = (CL)/λz. The pharmacokinetic population consisted of all subjects who had sufficient concentration-time data to enable the calculation of PK parameters for azacitidine.

End point type	Secondary

End point timeframe:

Subjects ≤20 kg, pre-dosing at C1 D5, D6 and post dose at C1 D7 at 5 min, 0.5 hours, 1, 4, and 6 hours; subjects > 20 kg, pre-dosing at C1 D5, D6 and D7, post dose on C1 D7 at 5 min, 0.5 hours, 1, 2, 4, 6 hours.

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Liters				
geometric mean (geometric coefficient of variation)	70.24 (± 83.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Leukemia-free Survival (LFS)

End point title	Kaplan Meier Estimate of Leukemia-free Survival (LFS)

End point description:

Leukemia-free survival was defined as the time from study enrollment until disease progression (identified as clinical progression/clinical relapse) or death. Subjects alive and disease progression free at the time of the statistical analysis were censored at the time they were last known to be alive. The Intent to Treat population included participants who were enrolled in the study regardless of whether or not they received any of the study treatment.

End point type	Secondary

End point timeframe:

From the time of study enrollment until the end of the safety run-in period; median follow-up time was 14.5 months (14.0 months to 36.0 months)

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	7[3]			
Units: months				
median (confidence interval 95%)	99999 (2.3 to 99999)			

Notes:

[3] - 99999 = Median not calculable; more than 50% of subjects had not had a LFS event at time of analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease Level (MRD) at Day 84

End point title	Minimal Residual Disease Level (MRD) at Day 84

End point description:

Minimal residual disease was analyzed using real-time polymerase chain reaction (RQ-PCR) of a subject specific fusion gene or aberration. MRD level was used to evaluate response based on following guideline:
- Molecular stabilization was defined as < 1 log decrease or increase of specific PCR marker from baseline.
- Molecular progression was defined as ≥ 1 log increase of specific PCR marker from baseline to a level of 5 x 10^-4 or above in the absence of signs of clinical relapse, in MRD-negative subjects. The rise had to be at least 1 log (10-fold) greater than previous sensitivity to a level of 5 x 10^-4 or above.
- Molecular improvement was defined as ≥ 1 log decrease of specific PCR marker from baseline.
- Clinical relapse was defined as at least 5% blasts in peripheral blood (PB) and/or BM and/or proven

histological extramedullary relapse.
The population included are the subjects with Day 84 information and completed treatment period

End point type	Secondary

End point timeframe:

Enrollment to Day 84

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	7[4]			
Units: MRD Level In Bone Marrow				
median (full range (min-max))	0.0041 (0.001 to 0.083)			

Notes:

[4] - Levels in bone marrow are for 4 subjects at day 84

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Overall Survival

End point title	Kaplan-Meier Estimate of Overall Survival

End point description:

Overall survival was defined as the time from study enrollment (safety run-in part) until death from any cause. Subjects alive at the time of the statistical analysis were censored at the time they were last known to be alive. The ITT population included participants who were enrolled in the study regardless of whether or not they received any of the study treatment.

End point type	Secondary

End point timeframe:

From the time of study enrollment until the end of the safety run-in period; up to 09 October 2019; median follow-up time was 14.5 months (range: 14.0 months to 36.0 months)

End point values	Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	7[5]			
Units: months				
median (confidence interval 95%)	99999 (2.4 to 99999)			

Notes:

[5] - 99999 = median overall survival not reached due to low number of events.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of the first dose of study drug up to and including 28 days after the last dose of study drug. Median treatment duration was 12.00 weeks, with minimum and maximum duration of 8.0 and 13.9 weeks, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Azacitidine 100mg/m^2

Reporting group description: -

Serious adverse events	Azacitidine 100mg/m^2		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Azacitidine 100mg/m^2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Pyrexia			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Irritability			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	10		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Procedural pain			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) Cardiac failure subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 1 / 7 (14.29%) 2		
Nervous system disorders Cerebral haemorrhage subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 2 / 7 (28.57%) 3 1 / 7 (14.29%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 3 / 7 (42.86%) 5 7 / 7 (100.00%) 20 3 / 7 (42.86%) 10		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1		
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Aphthous ulcer			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	5		
Mucous stools			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	11		
Stomatitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Pruritus			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Rash generalised			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Infections and infestations			
Device related infection			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	3		
Fungal skin infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Nasopharyngitis			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	2		
Viral tonsillitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	3		
Hypermagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Hyperphosphataemia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2015	• To address Germany's Federal Institute of Drugs and Medical Devices (BfArM) concerns regarding blood volumes, this amendment reduced the amount of blood being collected for PK. Each collection timepoint now required 1 mL of blood instead of 2 mL of blood. Also, for pediatric subjects weighing ≤ 20 kg, in order to minimize blood collection for these smaller children, only 5 timepoints were collected for PK assessments on Cycle 1 Day 7 (5 minutes postdose, 30 minutes postdose, 1 hour postdose, 4 hours postdose and 6 hours postdose), as opposed to the 7 collection timepoints required for subjects weighing > 20 kg (prior to dosing, 5 minutes postdose, 30 minutes postdose, 1 hour postdose, 2 hours postdose, 4 hours postdose and 6 hours postdose). • To address BfArM's concerns regarding dose reductions due to renal impairment and to be consistent with the azacitidine investigator's brochure, dose reduction guidelines based on fluctuations in serum creatinine were added to the protocol. The statement that dose adjustments were not allowed was removed. • In order to further minimize blood collection for this pediatric population, the blood volumes for hematology assessments were reduced from 2 mL to 1 mL at each timepoint. • The detailed guidance to destroy/return used or unused azacitidine vials was replaced with protocol template language that the clinical research associate was to review with the site the process for return/disposal/destruction of the IV vials.
14 May 2015	Clarification: the collection of the samples for confirmation of MR was to occur within 7 days of the detection of MR. Clarification: confirmation of MR required PB and BM MRD levels to be higher than the MRD level in the PB at the time of detection. Clarification: point of entry of subjects into the Long-term Follow-up Period (LTFUP) after 28 day safety follow-up was clarified for the Safety Run-in Part (SRI) and for the Randomized Part (RP).. Clarification: if HSCT was performed during the LTFU, a clinic visit had to occur pre-HSCT and at 3 and 6 months post-HSCT to have BM samples collected. Inclusion criteria regarding first CR1 for both SRI Part and RP were revised. For the RP, the collection of SAEs related to HSCT was added to the LTFU Period. Clarification: specific predrug eligibility criteria had to be verified prior to randomizing the subject into the RP. A 14-day visit window was added to Day 1 of Cycles 2 and 3 in the SRI Part and the EA of the RP. Clarification: the LTFU Period would last for 2 years from last subject enrolled/randomized. Guidances added for pregnancy testing for females ≥8 years or achieved menarche and for subjects <18 who reached the age of 18 while being treated that they had to agree to undergo physician approved reproductive education and discuss the side effects of study therapy with study doctor. Clarification: archived BM aspirate from initial diagnosis needed to be sent to the central laboratory in the RP only. Windows for PK blood sampling timepoints were added Clarification: in the Randomized Part, the central laboratory would use the BM aspirate sample from initial diagnosis to confirm the molecular aberrations Clarification: added about the IV solution preparation and administration time. Clarification: added about the treatment delay exception in start of 2nd and 3rd cycles due to renal toxicity

26 October 2017	• Molecular response (MR) at Day 84 (± 4 days) (or end of Cycle 3, if not the same date) was included as a secondary efficacy endpoint for the Safety Run-in Part. MR at end of Cycle 3 or Day 84 (± 4 days) (or end of Cycle 3, if not the same date) was added to evaluate the preliminary efficacy of the IP in the Safety Run-in Part prior to start of the Randomized Portion and to minimize subject exposure if the IP was not efficacious. • The secondary endpoints of changes in DNA methylation (assessments of BM samples using Nano-HELP assay) and MRD at 3 and 6 months post-HSCT were deleted in the Safety Run-in Part . A decision was made to evaluate these in the Randomized Phase only since sufficient patient information would be available for informative analysis. Deletion of these endpoints in a Safety Run-in would minimize unnecessary assessment and subject burden, especially in regard to frequent BM biopsies that are not standard of care. • Sample size of the Safety Run-in Part was increased from 12 to 18 to allow 6 additional subjects to enroll to assess preliminary efficacy prior to start of the Randomized Portion and to minimize subject exposure if the IP was not efficacious. 6 subjects had already been enrolled to the 100 mg/m2 dose of AZA. If this dose was deemed not safe or tolerable, 6 additional subjects were to be enrolled in a 75 mg/m2 cohort. Once the safe and tolerable dose level was determined, 6 further subjects were to be treated at the highest tolerated dose to gain preliminary efficacy, for a potential sample size of 18 patients (6 subjects in 100 mg/m2 cohort, 6 subjects in the 75 mg/m2 cohort, 6 subjects to assess preliminary efficacy). The Long-term Follow-up was reduced to 1 year from the last dose of IP instead of 2 years from last subject enrolled since there were no safety concerns and 1 year of information post last dose would provide enough safety information and should allow sufficient time to follow the subjects through HSCT.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The Randomized Part of the study was not conducted. The study was transitioned to a single-arm study (N=20) Phase 2 non-Celgene sponsored study.

Notes: