

**Clinical trial results:****A Phase 2, Multicenter, Open-label Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Activity of Azacitidine and to Compare Azacitidine to Historical Controls in Pediatric Subjects With Newly Diagnosed Advanced Myelodysplastic Syndrome or Juvenile Myelomonocytic Leukemia Before Hematopoietic Stem Cell Transplantation****Summary**

EudraCT number	2014-002388-13
Trial protocol	DE ES GB IE AT CZ BE IT SE DK NL FR
Global end of trial date	23 May 2019

**Results information**

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

**Trial information****Trial identification**

Sponsor protocol code	AZA-JMML-001
-----------------------	--------------

**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02447666
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	Bouchra Benettaib, MD, 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	23 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2019
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the treatment effect on response rate [myelodysplastic syndrome (MDS): either complete remission [CR], partial remission [PR], or marrow CR; juvenile myelomonocytic leukemia (JMML): either clinical complete remission [cCR] or clinical partial remission [cPR]]; at Cycle 3 Day 28 and to compare against standard therapy using a matched-pairs analysis of historical data.

Protection of trial subjects:

Informed Consent, Patient Confidentiality, Archiving of Essential Documents

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 2015
Long term follow-up planned	Yes
Long term follow-up rationale	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	Czech Republic: 3
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 1
Worldwide total number of subjects	28
EEA total number of subjects	27

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)	9
Children (2-11 years)	12
Adolescents (12-17 years)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 18 sites in the Czech Republic, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden and Switzerland.

### Pre-assignment

Screening details:

The study consisted of 2 cohorts: subjects aged 1 month to less than 18 years of age with newly diagnosed MDS or with newly diagnosed JMML prior to hematopoietic stem cell transplantation (HSCT) were enrolled in Stage 1 of the 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

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MDS: Azacitidine

Arm description:

Subjects with myelodysplastic syndrome received azacitidine 75 mg/m<sup>2</sup>, either by intravenous (IV) infusion or by subcutaneous (SC) injection, on Days 1 to 7 of each 28-day treatment cycle for a minimum of 3 cycles and a maximum of 6 cycles, unless disease progression occurred.

Arm type	Experimental
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	Vidaza
Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Azacitidine 75 mg/m<sup>2</sup>, either by IV infusion or by SC injection, on Days 1 to 7 of each 28-day treatment cycle

<b>Arm title</b>	JMML: Azacitidine
------------------	-------------------

Arm description:

Subjects with JMML received azacitidine 75 mg/m<sup>2</sup>, either by IV infusion or by SC injection on Days 1 to 7 of each 28-day treatment cycle for a minimum of 3 cycles and a maximum of 6 cycles, unless disease progression occurred.

Arm type	Experimental
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	Vidaza
Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Azacitidine 75 mg/m<sup>2</sup>, either by IV infusion or by SC injection, on Days 1 to 7 of each 28-day treatment cycle

<b>Number of subjects in period 1</b>	MDS: Azacitdine	JMML: Azacitidine
Started	10	18
Completed	7	15
Not completed	3	3
Physician decision	2	-
Adverse event, non-fatal	1	1
Progressive Disease	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	MDS: Azacitidine
-----------------------	------------------

Reporting group description:

Subjects with myelodysplastic syndrome received azacitidine 75 mg/m<sup>2</sup>, either by intravenous (IV) infusion or by subcutaneous (SC) injection, on Days 1 to 7 of each 28-day treatment cycle for a minimum of 3 cycles and a maximum of 6 cycles, unless disease progression occurred.

Reporting group title	JMML: Azacitidine
-----------------------	-------------------

Reporting group description:

Subjects with JMML received azacitidine 75 mg/m<sup>2</sup>, either by IV infusion or by SC injection on Days 1 to 7 of each 28-day treatment cycle for a minimum of 3 cycles and a maximum of 6 cycles, unless disease progression occurred.

Reporting group values	MDS: Azacitidine	JMML: Azacitidine	Total
Number of subjects	10	18	28
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	1	10	11
Children (2-11 years)	2	8	10
Adolescents (12-17 years)	7	0	7
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	11.16	2.38	
standard deviation	± 4.862	± 1.685	-
Gender Categorical Units: Subjects			
Female	4	7	11
Male	6	11	17
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	10	16	26
Not Reported	0	1	1
Unknown	0	0	0
Primary Race Units: Subjects			
American Indian	0	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	10	16	26

Not Collected or Reported	0	1	1
Other	0	1	1
Newly Diagnosed Advanced Myelodysplastic Syndrome Diagnosis			
Myelodysplastic syndrome in children can be divided into primary and secondary. If no cause can be identified, it is called primary MDS. Myelodysplastic syndrome after prior chemotherapy or radiation therapy, after prior acquired aplastic anemia, or in inherited bone marrow (BM) failure disorders is classified as secondary MDS.			
Units: Subjects			
Primary	10	0	10
Secondary	0	0	0
Other	0	18	18
Newly Diagnosed Advanced Myelodysplastic Syndrome Classification			
Newly diagnosed advanced primary or secondary MDS, with one of the following: - Refractory anemia with excess blasts (RAEB): 2% to 19% blasts in peripheral blood (PB) or 5% to 19% blasts in bone marrow (BM). - Refractory anemia with excess blasts in transformation (RAEB-t): 20% to 29% of blasts in PB or BM. - Secondary MDS presenting as Chronic myelomonocytic leukemia (CMML) without increase in blasts but with chromosomal abnormality			
Units: Subjects			
Refractory Anemia with Excess Blasts (RAEB)	6	0	6
RAEB in Transformation (RAEB-t)	4	0	4
2ndary MDS Presenting as CMML	0	0	0
Other	0	18	18
Juvenile Myelomonocytic Leukemia Diagnostics			
Newly diagnosed JMML, with one of the following: - somatic mutation in PTPN11-gene (PTPN11) - somatic mutation in (KRAS-gene) KRAS - somatic mutation in (NRAS - gene) NRAS and (fetal hemoglobin) HbF % > 5x normal value for age - clinical diagnosis of neurofibromatosis Type 1.			
Units: Subjects			
Somatic Mutations in PTPN 11	0	13	13
Somatic Mutation in KRAS	0	1	1
Somatic Mutation in NRAS and HbF% >5 x's Normal	0	3	3
Clinical Diagnosis of Neurofibromatosis Type 1	0	1	1
Other	10	0	10
Methylation Class			
Unsupervised cluster analyses of methylation profiles in JMML samples, using the 1,000 most variables JMML differentially methylated probe (DMPs) mapping to CpG islands to identify high, intermediate or low methylation classes. JMML methylation class clusters into 3 subgroups ie., high, intermediate and low.			
Units: Subjects			
High	0	11	11
Intermediate	0	5	5
Low	0	2	2
MDS: Not Done	10	0	10
Time From Initial Diagnosis			
Units: days			
median	7.5	24.5	
full range (min-max)	1.0 to 25.0	1.0 to 73.0	-

## End points

### End points reporting groups

Reporting group title	MDS: Azacitidine
Reporting group description: Subjects with myelodysplastic syndrome received azacitidine 75 mg/m <sup>2</sup> , either by intravenous (IV) infusion or by subcutaneous (SC) injection, on Days 1 to 7 of each 28-day treatment cycle for a minimum of 3 cycles and a maximum of 6 cycles, unless disease progression occurred.	
Reporting group title	JMML: Azacitidine
Reporting group description: Subjects with JMML received azacitidine 75 mg/m <sup>2</sup> , either by IV infusion or by SC injection on Days 1 to 7 of each 28-day treatment cycle for a minimum of 3 cycles and a maximum of 6 cycles, unless disease progression occurred.	

### Primary: MDS Cohort: Percentage of Subjects with a Confirmed Response at Cycle 3, Day 28 Based on Central Review

End point title	MDS Cohort: Percentage of Subjects with a Confirmed Response at Cycle 3, Day 28 Based on Central Review <sup>[1][2]</sup>
End point description: The response rate was defined as the percentage of subjects with a confirmed complete remission (CR), partial remission (PR) or marrow complete remission (mCR), according to modified International Working Group (IWG) response criteria, adapted to pediatric reference values at 3 months. Response must have been sustained for at least 4 weeks either in the 4-week period preceding or succeeding Cycle 3 Day 28. A CR = $\leq 5\%$ myeloblasts in bone marrow (BM), and peripheral blood (PB) Hemoglobin (hgb) $\geq 9$ g/dL (1-12 months), $\geq 10$ g/dL (13 months-11years), $\geq 11$ g/dL ( $\geq 12$ months) Platelets $\geq 100 \times 10^9/L$ Neutrophils $\geq 1.0 \times 10^9/L$ Blasts 0% PR= CR criteria if abnormal before treatment except BM blasts decreased by $\geq 50\%$ over pretreatment but still $> 5\%$ ; Cellularity and morphology not relevant for PB; mCR: BM $\leq 5\%$ myeloblasts and decrease by $\geq 50\%$ over pretreatment. Intent to treat population = all subjects enrolled regardless of whether or not they received any dose of the study drug.	
End point type	Primary
End point timeframe: Response was assessed at Cycle 3, Day 28; up to the data cut-off date of 13 March 2019; median treatment duration was 12 weeks (range: 5.0 to 12.7 weeks).	

#### 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.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	MDS: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of Subjects				
number (confidence interval 95%)	0.0 (0.0 to 30.8)			

## Statistical analyses



**Primary: JMML Cohort: Percentage of Subjects with a Confirmed Response at Cycle 3, Day 28 Based on Central Review**

End point title	JMML Cohort: Percentage of Subjects with a Confirmed Response at Cycle 3, Day 28 Based on Central Review <sup>[3][4]</sup>
-----------------	--

## End point description:

Response = the percentage of subjects with a sustained clinical CR (cCR) or cPR according to the International JMML response criteria at 3 months. Response had to be sustained for at least 4 weeks either in the 4-week period preceding or succeeding Cycle 3 Day 28. A cCR = WBC:  $\geq 3.0 - 15.0 \times 10^9/L$  Myeloid, erythroid precursors and blasts in PB: 0-1% Platelet count  $\geq 100 \times 10^9/L$  BM contains  $<5\%$  blast cells, no splenomegaly by sonography, no extramedullary leukemic infiltration in an organ cPR = WBC: decreased by  $\geq 50\%$  over pretreatment but still  $>15 \times 10^9/L$  Myeloid, erythroid precursors and blasts in PB decreased by  $\geq 50\%$  over pretreatment but yet  $\geq 2\%$  Platelet count =  $\geq 20 \times 10^9/L$  platelets, absolute increase of  $\geq 30 \times 10^9/L$ ; those with  $< 20 \times 10^9/L$  platelets: increase by  $\geq 100\%$  and  $> 20 \times 10^9/L$  Blast cells decreased by  $\geq 50\%$  over pretreatment but  $\geq 5.0\%$  Splenic clinical evaluation and  $\geq 25\%$  decrease by length No extramedullary leukemic infiltration. ITT Population

End point type	Primary
----------------	---------

## End point timeframe:

Response was assessed at Cycle 3, Day 28; up to the data cut-off date of 13 March 2019; median treatment duration was 12.29 weeks (range: 4.0 to 30.6 weeks).

## Notes:

[3] - 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.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage				
number (confidence interval 95%)	50.0 (26.0 to 74.0)			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: MDS Cohort: Number of Subjects who Achieved a Cytogenetic Response at Cycle 3 Day 28 Based on Central Review**

End point title	MDS Cohort: Number of Subjects who Achieved a Cytogenetic Response at Cycle 3 Day 28 Based on Central Review <sup>[5]</sup>
-----------------	---

## End point description:

The cytogenetic response was defined as the number of subjects with complete disappearance of the chromosomal abnormality without appearance of new ones according to the modified IWG 2006 response criteria for MDS. Subjects with a response observed after hematopoietic stem cell transplantation (HSCT) were censored. Responses occurring after start of a new anticancer therapy were censored. ITT population evaluable for cytogenetic response.

End point type	Secondary
----------------	-----------

## End point timeframe:

Response was assessed at Cycle 3, Day 28; up to the data cut-off date of 13 March 2019; for MDS subjects, median treatment duration was 12 weeks (range: 5.0 to 12.7 weeks).

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: No statistical analysis was performed.

End point values	MDS: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
number (not applicable)				
Definite Cytogenetic Response	1			
No Cytogenetic Response	6			
Missing Cytogenetic Response	3			

## Statistical analyses

No statistical analyses for this end point

## Secondary: JMML Cohorts: Number of Subjects who Achieved a Genetic and Molecular Response at Cycle 3 Day 28 Based on Central Review

End point title	JMML Cohorts: Number of Subjects who Achieved a Genetic and Molecular Response at Cycle 3 Day 28 Based on Central Review <sup>[6]</sup>
-----------------	---

End point description:

The cytogenetic response is defined as the number of subjects with complete disappearance of the chromosomal abnormality without appearance of new ones. A molecular response rate was defined as the number of subjects with absence of somatic mutations related to JMML. ITT population evaluable for cytogenetic and molecular response.

End point type	Secondary
----------------	-----------

End point timeframe:

Response was assessed at Cycle 3, Day 28; up to data cut-off date of 13 March 2019; median treatment duration was 12.29 weeks (range: 4.0 to 30.6 weeks).

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: No statistical analysis was performed.

End point values	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Subjects				
number (not applicable)				
Genetic Response	2			
No Genetic Response	14			
Missing Genetic Response	2			
Molecular Response	2			

## Statistical analyses

No statistical analyses for this end point

### Secondary: MDS Cohort: Kaplan-Meier Estimate of Duration of Response Based on Central Review

End point title	MDS Cohort: Kaplan-Meier Estimate of Duration of Response Based on Central Review <sup>[7]</sup>
-----------------	--

End point description:

Duration of response (DoR) consisted of only the subjects who achieved a response (CR, PR or marrow CR) and was defined as the time from first observed response until either disease progression or any cause of death. Only subjects with a response observed before HSCT (or a new anticancer therapy) were included in the analysis. If no relapse, PD, or death was observed, the duration of response was censored at the last response assessment date that the subject was known to be progression-free.

End point type	Secondary
----------------	-----------

End point timeframe:

Time from first observed response until disease progression until any cause of death; up to data cut-off date of 13 March 2019; median treatment duration was 12 weeks (range: 5.0 to 12.7 weeks).

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis was performed.

End point values	MDS: Azacitdine			
Subject group type	Reporting group			
Number of subjects analysed	1 <sup>[8]</sup>			
Units: Months				
median (confidence interval 95%)	99999 (-99999 to 99999)			

Notes:

[8] - 99999 = not estimable due to a HSCT or another treatment the subject received.

## Statistical analyses

No statistical analyses for this end point

### Secondary: JMML Cohort: Kaplan-Meier Estimate of Duration of Response Based on Central Review

End point title	JMML Cohort: Kaplan-Meier Estimate of Duration of Response Based on Central Review <sup>[9]</sup>
-----------------	---

End point description:

Duration of response consisted of only the subjects who achieved a response and was defined as the time from the first overall response (clinical CR, cPR), whichever occurred first until either disease progression or any cause of death. ITT Population. Only subjects with a response observed before HSCT (or a new anticancer therapy) were included in the analysis. If no relapse, progressive disease (PD), or death was observed, the duration of response was censored at the last response assessment date that the subject was known to be progression-free.

End point type	Secondary
----------------	-----------

End point timeframe:

Time from first observed response until disease progression until any cause of death; up to data cut-off date of 13 March 2019; median treatment duration was 12.29 weeks (range: 4.0 to 30.6 weeks).

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistical analysis was performed.

<b>End point values</b>	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	18 <sup>[10]</sup>			
Units: Days				
median (confidence interval 95%)	99999 (-99999 to 99999)			

Notes:

[10] - 99999 = Not estimable due a HSCT or another treatment the subject received.

## Statistical analyses

No statistical analyses for this end point

### Secondary: MDS Cohort: Time to Response Based on Central Review

End point title	MDS Cohort: Time to Response Based on Central Review <sup>[11]</sup>
-----------------	--

End point description:

Time to response (TTR) was defined as the time from first study dose day until a response (CR, PR or marrow CR for MDS whichever occurred first). ITT population. Only subjects with a response observed before HSCT (or a new anticancer therapy) were included in the analysis with the median TTR across the subjects presented. Responses that occurred after start of a new anticancer therapy were not considered.

End point type	Secondary
----------------	-----------

End point timeframe:

Response was assessed following every treatment cycle until treatment discontinuation; up to data cut-off date of 13 March 2019; median treatment duration was 12 weeks (range: 5.0 to 12.7 weeks).

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

<b>End point values</b>	MDS: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[12]</sup>			
Units: Months				
median (confidence interval 95%)	2.76 (-99999 to 99999)			

Notes:

[12] - 99999 = Not estimable due to the low number of responders

## Statistical analyses

No statistical analyses for this end point

### Secondary: JMML Cohort: Time to Response Based on Central Review

End point title	JMML Cohort: Time to Response Based on Central Review <sup>[13]</sup>
-----------------	---

End point description:

Time to response was defined as the time from first study dose day until a response (cCR, cPR whichever occurred first). ITT population. Only subjects with a response observed before HSCT (or before a new anticancer therapy) were included in the analysis with the median TTR across the subjects presented. Responses that occurred after start of a new anticancer therapy were not considered.

End point type	Secondary
----------------	-----------

End point timeframe:

Response was assessed following every treatment cycle until treatment discontinuation; up to data cut-off date of 13 March 2019; median treatment duration was 12.29 weeks (range: 4.0 to 30.6 weeks).

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Days				
median (confidence interval 95%)	1.20 (0.95 to 1.87)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: MDS Cohort: Kaplan Meier Estimate of Time to Progression

End point title	MDS Cohort: Kaplan Meier Estimate of Time to Progression <sup>[14]</sup>
-----------------	--

End point description:

Time to progression (TTP) was defined as the time from first study dose day until either disease progression or death due to progression. For subjects who were alive at the time of the analysis without an observed disease progression: • Subjects without an anticancer therapy and without HSCT were censored at the time of last date known alive • Subjects with HSCT were censored at the earliest date between HSCT and last date known alive. • Subjects who started an anticancer therapy but without HSCT were censored at the time of the last disease assessment before start of the anticancer therapy.

End point type	Secondary
----------------	-----------

End point timeframe:

Time from first study dose day to either disease progression or death; up to the data cut-off date of 13 March 2019; median treatment duration was 12 weeks (range: 5.0 to 12.7 weeks).

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	MDS: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Months				
median (confidence interval 95%)	0.97 (0.95 to 2.04)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: JMML Cohort: Kaplan Meier Estimate of Time to Progression

End point title	JMML Cohort: Kaplan Meier Estimate of Time to Progression <sup>[15]</sup>
-----------------	---

End point description:

Time to progression was defined as the time from first study dose day until either disease progression or death due to progression. For subjects who were alive at the time of the analysis without an observed disease progression: • Subjects without an anticancer therapy and without HSCT were censored at the time of last date known alive • Subjects with HSCT were censored at the earliest date between HSCT and last date known alive. • Subjects who started an anticancer therapy but without HSCT were censored at the time of the last disease assessment before start of the anticancer therapy.

End point type	Secondary
----------------	-----------

End point timeframe:

Time from first study dose day to either disease progression or death; up to data cut-off date of 13 March 2019; median treatment duration was 12.29 weeks (range: 4.0 to 30.6 weeks).

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	18 <sup>[16]</sup>			
Units: Months				
median (confidence interval 95%)	99999 (0.95 to 99999)			

Notes:

[16] - 99999 = Not estimable due to fewer than half of the subjects having disease progression.

## Statistical analyses

No statistical analyses for this end point

## Secondary: MDS Cohort: Kaplan Meier Estimate of Leukemia-Free Survival (LFS)

End point title	MDS Cohort: Kaplan Meier Estimate of Leukemia-Free Survival (LFS) <sup>[17]</sup>
-----------------	---

End point description:

Leukemia-free survival was defined as the time from HSCT date until leukemia progression or death for subjects receiving a HSCT only. Subjects alive and leukemia-free at the time of the analysis were censored at the time of their last disease assessment. Subjects were also censored at the time of starting a new anticancer therapy if having not previously had a leukemia progression. ITT population was defined as all subjects enrolled into the study regardless of whether or not they received any dose of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

LFS was assessed up to data cut-off date of 24 May 2019; the median LFS follow up time was 22.47 months

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

<b>End point values</b>	MDS: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[18]</sup>			
Units: Months				
median (confidence interval 95%)	99999 (13.60 to 99999)			

Notes:

[18] - 99999 = Not Estimable due to over 50% of subjects being censored

## Statistical analyses

No statistical analyses for this end point

## Secondary: JMML Cohort: Kaplan Meier Estimate of Leukemia-Free Survival

End point title	JMML Cohort: Kaplan Meier Estimate of Leukemia-Free
-----------------	---

End point description:

Leukemia-free survival was defined as the time from HSCT date until leukemia progression or death for subjects receiving a HSCT only. Subjects alive and leukemia-free at the time of the analysis were censored at the time of their last disease assessment. Subjects were also censored at the time of starting a new anticancer therapy if having not previously had a leukemia progression. ITT population was defined as all subjects enrolled into the study regardless of whether or not they received any dose of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

LFS was assessed up to data cut-off date of 24 May 2019; the median LFS follow up time was 20.99 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

<b>End point values</b>	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	17 <sup>[20]</sup>			
Units: Months				
median (confidence interval 95%)	99999 (-99999 to 99999)			

Notes:

[20] - 99999- median was not estimable due to over 50% of subjects being censored.

## Statistical analyses

No statistical analyses for this end point

## Secondary: MDS Cohort: Kaplan Meier Estimate of Overall Survival

End point title	MDS Cohort: Kaplan Meier Estimate of Overall Survival <sup>[21]</sup>
-----------------	---

End point description:

Overall survival was defined as the time from first study dose day until death from any cause. Subjects alive at the time of analysis were censored at the time they were last known to be alive. ITT population was defined as all subjects enrolled into the study regardless of whether or not they received any dose of the study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

From date of the first dose of study drug until death; up to the data-cut off date of 24 May 2019;  
median follow-up time was 25.72 months

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	MDS: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[22]</sup>			
Units: Months				
median (confidence interval 95%)	99999 (18.37 to 99999)			

Notes:

[22] - 99999 = not estimable due to the majority of subjects being censored.

## Statistical analyses

No statistical analyses for this end point

## Secondary: JMML Cohort: Kaplan Meier Estimate of Overall Survival

End point title	JMML Cohort: Kaplan Meier Estimate of Overall Survival <sup>[23]</sup>
-----------------	--

End point description:

Overall Survival (OS) was defined as the time from first study dose day until death from any cause. Subjects alive at the time of analysis were censored at the time they were last known to be alive. ITT population was defined as all subjects enrolled into the study regardless of whether or not they received any dose of the study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

From date of the first dose of study drug until death; up to the data cut-off date of 24 May 2019;  
median follow-up time was 25.43 months

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	18 <sup>[24]</sup>			
Units: Months				
median (confidence interval 95%)	99999 (-99999 to 99999)			

Notes:

[24] - 99999 = median not estimable due to the majority of subjects alive at the time of the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: MDS Cohort: Percentage of Subjects Who Received a Hematopoietic



## Stem Cell Transplant (HSCT)

End point title	MDS Cohort: Percentage of Subjects Who Received a Hematopoietic Stem Cell Transplant (HSCT) <sup>[25]</sup>
-----------------	---

End point description:

The rate of HSCT was defined as the percentage of subjects who received study dose and underwent a HSCT of the subjects in the ITT Population. ITT Population was defined as all subjects enrolled into the study regardless of whether or not they received any dose of the study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

From the date of first dose of study drug to the end of the follow-up period; up to the data-cut off date of 13 March 2019

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

<b>End point values</b>	MDS: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage				
number (confidence interval 95%)	100.0 (69.2 to 100.0)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: JMML Cohort: Percentage of Subjects Who Received a HSCT

End point title	JMML Cohort: Percentage of Subjects Who Received a HSCT <sup>[26]</sup>
-----------------	---

End point description:

The rate of HSCT was defined as percentage of subjects who received study drug and received a HSCT during the conduct of this study in the ITT population. ITT Population was defined as all subjects enrolled into the study regardless of whether or not they received any dose of the study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

From the date of the first dose of study drug to the date of the HSCT; up to the data cut-off date of 13 March 2019.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

<b>End point values</b>	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of Subjects				
number (confidence interval 95%)	94.4 (72.7 to 99.9)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: MDS Cohort: Time to First Hematopoietic Stem Cell Transplant

End point title	MDS Cohort: Time to First Hematopoietic Stem Cell
-----------------	---

End point description:

Time to HSCT was defined as the time from first study dose day until HSCT date. Subjects not receiving a HSCT were censored at the time of the analysis. ITT Population was defined as all subjects enrolled into the study regardless of whether or not they received any dose of the study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Date of first dose of study drug to the date the subjects received the HSCT; up to the data cut-off date of 13 March 2019

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	MDS: Azacitdine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Months				
median (confidence interval 95%)	3.76 (2.79 to 4.73)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: JMML Cohort: Time to First Hematopoietic Stem Cell Transplant

End point title	JMML Cohort: Time to First Hematopoietic Stem Cell
-----------------	--

End point description:

Time to HSCT was defined as the time from first study dose day until HSCT date. Subjects not receiving a HSCT were censored at the time of the analysis. ITT Population was defined as all subjects enrolled into the study regardless of whether or not they received any dose of the study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Date of first dose of study drug to the date the subject received a HSCT; up to the data cut-off date of 13 March 2019

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was performed.

End point values	JMML: Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Months				
median (confidence interval 95%)	4.63 (3.91 to 6.77)			

## 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:

TEAEs are adverse events that started or worsened between the date of first study drug dose and up to 28 days after the date of last dose. TEAEs were recorded by the Investigator from the day of the first dose of IP until 28 days after the last dose of azacitidine and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to azacitidine. The severity of AEs were graded 1 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (version 4.0) and the severity was assessed by the investigator as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or death (grade 5). A serious adverse event (SAE) is any: • Death; • Life-threatening event; • Any inpatient hospitalization or prolongation of existing hospitalization; • Persistent or significant disability or incapacity; • Congenital anomaly or birth defect; • Any other important medical event

End point type	Secondary
----------------	-----------

End point timeframe:

From date of first dose of study drug up to 28 days after the last dose of azacitidine and for those SAEs made known to the investigator at any time during the study. Median treatment duration for MDS subjects = 12 weeks and 12.29 weeks for JMML subjects.

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: Subjects				
≥ 1 TEAE	10	18		
≥1 Grade (GR) 3-4 TEAE	7	10		
≥ 1 TEAE Related to Azacitidine (AZA)	7	10		
≥ 1 GR 3-4 TEAE Related to AZA	3	6		
≥ 1 Serious TEAE	4	12		
≥1 Serious TEAE Related to AZA	2	3		
≥ 1 TEAE Leading to Dose Reduction of AZA	0	0		

≥1 Serious TEAE leading to Dose Reduction of AZA	0	0		
≥ 1 TEAE Leading to Dose Interruption of AZA	0	0		
≥1 Serious TEAE leading to Dose Interrupt of AZA	0	0		
≥ 1 TEAE Leading to Discontinuation of AZA	1	2		
≥1 Serious TEAE leading to Discontinuation of AZA	1	2		
≥ At Least 1 TEAE Leading to Death	0	0		

## 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) evaluable population consisted of all subjects who received at least 1 dose of study drug and had at least 1 measurable concentration of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Subjects ≤20 kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects >20 kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1797.5 (± 133.6)	1066.3 (± 215.3)		

## 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 evaluable population consisted of all subjects who received at least 1 dose of study drug and had at least 1 measurable concentration of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Subjects  $\leq 20$  kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects  $> 20$  kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: hours				
median (full range (min-max))	0.083 (0.00 to 0.50)	0.083 (0.03 to 0.33)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to the Last Quantifiable Time Point (AUC0-t) of Azacitidine

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to the Last Quantifiable Time Point (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 evaluable population consisted of all subjects who received at least 1 dose of study drug and had at least 1 measurable concentration of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Subjects  $\leq 20$  kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects  $> 20$  kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	629.069 ( $\pm$ 123.1)	386.897 ( $\pm$ 149.4)		

### 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 evaluable population consisted of all subjects who received at least 1 dose of study drug and had at least 1 measurable concentration of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Subjects ≤20 kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects >20 kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	634.840 (± 122.2)	394.395 (± 145.9)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Plasma Concentration-time Curve from Time Zero to Infinity (AUC<sub>∞</sub>) of Azacitidine

End point title	Area Under the Plasma Concentration-time Curve from Time Zero to Infinity (AUC <sub>∞</sub> ) 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:  $AUC_{\infty} = AUC_t + (C_t/\lambda_z)$ , where  $C_t$  is the last quantifiable concentration. No AUC extrapolation will be performed with unreliable  $\lambda_z$ . If AUC% Ext is > 25%, AUC<sub>∞</sub> will not be reported. The pharmacokinetic evaluable population consisted of all subjects who received at least 1 dose of study drug and had at least 1 measurable concentration of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Subjects ≤20 kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects >20 kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	606.855 (± 131.6)	240.212 (± 76.5)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Terminal Phase Half-life (t<sub>1/2</sub>) of Azacitidine

End point title	Terminal Phase Half-life (t <sub>1/2</sub> ) of Azacitidine
-----------------	---

End point description:

Terminal phase half-life, was calculated according to the following equation:  $t_{1/2} = 0.693/\lambda_z$ . The pharmacokinetic evaluable population consisted of all subjects who received at least 1 dose of study drug and had at least 1 measurable concentration of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Subjects ≤20 kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects >20 kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: hours				
geometric mean (geometric coefficient of variation)	0.433 (± 22.7)	0.286 (± 58.4)		

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Apparent total clearance, calculated as  $\text{Dose}/\text{AUC}_{\infty}$ . The pharmacokinetic evaluable population consisted of all subjects who received at least 1 dose of study drug and had at least 1 measurable concentration of study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Subjects ≤20 kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects >20 kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: L/h				
geometric mean (geometric coefficient of variation)	166.434 ( $\pm$ 135.6)	148.298 ( $\pm$ 104.2)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Apparent Volume of Distribution (V<sub>z</sub>/F) of Azacitidine

End point title	Apparent Volume of Distribution (V <sub>z</sub> /F) of Azacitidine
End point description: Apparent volume of distribution of azacitidine was calculated according to the equation $V_z = (CL)/\lambda_z$ . The PK population consisted of all subjects who received at least one dose of azacitidine and had at least one measurable concentration of azacitidine.	
End point type	Secondary
End point timeframe: Subjects $\leq 20$ kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects $> 20$ kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.	

End point values	MDS: Azacitidine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: Liters				
geometric mean (geometric coefficient of variation)	103.873 ( $\pm$ 122.0)	61.119 ( $\pm$ 125.8)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Terminal Phase Rate Constant ( $\lambda_z$ ) of Azacitidine

End point title	Terminal Phase Rate Constant ( $\lambda_z$ ) of Azacitidine
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 evaluable population consisted of all subjects who received at least 1 dose of study drug and had at least 1 measurable concentration of study drug.	
End point type	Secondary



---

End point timeframe:

Subjects ≤20 kg, Day 7 PK obtained post-dose: 5 min (IV treated), 15 min (SC treated), 30 min and 1, 4, 6, and 8 hours; subjects >20 kg, on Day 7: 1 hour pre-dose and post-dose = 5 min (IV treated), 15 min (SC treated), 30 min and 1, 2, 4, 6, and 8 hours.

---

End point values	MDS: Azacitdine	JMML: Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	18		
Units: L/h				
geometric mean (geometric coefficient of variation)	1.822 (± 48.4)	2.028 (± 83.1)		

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From date of first dose of study drug up to 28 days after the last dose of azacitidine and for those SAEs made known to the investigator at any time during the study. Median treatment duration for MDS subjects = 12 weeks and 12.29 weeks for JMML subjects.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

### Reporting groups

Reporting group title	MDS Cohort: Azacitidine
-----------------------	-------------------------

Reporting group description:

Subjects with MDS received azacitidine 75 mg/m<sup>2</sup>, either by intravenous infusion or by subcutaneous injection, on Days 1 to 7 of each 28-day treatment cycle for a minimum of 3 cycles and a maximum of 6 cycles, unless disease progression occurred.

Reporting group title	JMML Cohort: Azacitidine
-----------------------	--------------------------

Reporting group description:

Subjects with JMML received azacitidine 75 mg/m<sup>2</sup>, either by intravenous infusion or by subcutaneous injection, on Days 1 to 7 of each 28-day treatment cycle for a minimum of 3 cycles and a maximum of 6 cycles, unless disease progression occurred.

Serious adverse events	MDS Cohort: Azacitidine	JMML Cohort: Azacitidine	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	12 / 18 (66.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Juvenile chronic myelomonocytic leukaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaesthetic complication pulmonary			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			

subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	5 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenomegaly			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 18 (11.11%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	2 / 18 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	MDS Cohort: Azacitidine	JMML Cohort: Azacitidine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	17 / 18 (94.44%)	
Vascular disorders			
Haematoma			

subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Face oedema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Generalised oedema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pain			

subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	10 / 18 (55.56%)	
occurrences (all)	4	33	
Vessel puncture site haematoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 10 (10.00%)	4 / 18 (22.22%)	
occurrences (all)	1	4	
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 18 (11.11%)	
occurrences (all)	2	5	
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pharyngeal erythema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory distress			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Rhinorrhoea			



subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Tachypnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Investigations			
Blood albumin decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Blood fibrinogen decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Candida test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Enterococcus test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Staphylococcus test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Viral test positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Contusion			

subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Head injury			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Joint dislocation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pericarditis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 10 (60.00%)	7 / 18 (38.89%)	
occurrences (all)	24	41	
Coagulopathy			

subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Hilar lymphadenopathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Histiocytosis haematophagic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	11	0	
Lymphadenopathy			
subjects affected / exposed	0 / 10 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	3	
Lymphopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	5	0	
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 18 (16.67%)	
occurrences (all)	1	3	
Thrombocytopenia			
subjects affected / exposed	4 / 10 (40.00%)	5 / 18 (27.78%)	
occurrences (all)	25	40	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Eye disorders			
Eye pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	5	
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	3 / 10 (30.00%)	4 / 18 (22.22%)	
occurrences (all)	3	5	
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	4 / 18 (22.22%)	
occurrences (all)	0	9	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gingival bleeding			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gingival hypertrophy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Mouth haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nausea			

subjects affected / exposed	3 / 10 (30.00%)	2 / 18 (11.11%)	
occurrences (all)	3	3	
Oral mucosal erythema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Periodontal disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Periodontal inflammation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Proctalgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Rectal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	3 / 10 (30.00%)	4 / 18 (22.22%)	
occurrences (all)	5	6	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hepatic failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	1 / 18 (5.56%) 5	
Skin and subcutaneous tissue disorders			
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 18 (11.11%) 3	
Dermatitis bullous subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
Petechiae subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	2 / 18 (11.11%) 2	
Pruritus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 18 (16.67%) 3	
Pruritus generalised subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 18 (16.67%) 3	
Rash subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 18 (11.11%) 2	
Rash erythematous subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 18 (0.00%) 0	
Rash macular subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 18 (11.11%) 2	
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
Rash papular subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 18 (5.56%) 1	
Rash pruritic			

subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Infections and infestations			
Anal candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Candida infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Clostridium difficile infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dermatitis infected			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Febrile infection			

subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Oral infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Otitis externa			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Rhinitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Fluid retention			
subjects affected / exposed	0 / 10 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Hyperkalaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	



Hyperuricaemia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	4	
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Malnutrition			
subjects affected / exposed	1 / 10 (10.00%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2014	<p>As an added precaution to minimize harm, treatment discontinuation guidelines for subjects who, after 3 cycles, were responders to azacitidine and who had a neutrophil count below <math>0.5 \times 10^9/L</math> on Cycle 3 Day 28, or on Day 1 of Cycle 5 or 6. Subjects who met the criteria were to be discontinued from therapy and prepared for transplant. • A 14-day window was specified from diagnosis to the screening visit, was from the second (the latest) BM biopsy. The first BM exam did not need to be within 14 days of the screening visit. • In order to address regulatory concerns regarding blood volumes, the amount of blood collected for PK was reduced. Each collection time point required 1 mL of blood instead of 2 mL. For pediatric subjects who weighed <math>\leq 20</math> kg, to minimize blood collection for smaller children, only 5 time points were collected for PK assessments. • Reduced blood volumes for hematology and chemistry assessments from 2 mL to 1 mL at each time point. Removed requirement to draw 2 mL of blood for the PB smear slide. • Since the risk of disease transformation does not apply to JMML, the requirement for JMML subjects to have a BM aspirate within 14 days of the screening visit was removed. • Due to its rarity, subjects with NF-1 mutation without clinical symptoms were excluded. • Added instructions for storage of reconstituted AZA for SC administration for immediate use and for delayed use. Instructions for administration of reconstituted AZA for IV use was added to clarify the administration window for reconstituted product. • In order to address regulatory concerns for renal impairment, dose reduction guidelines based on fluctuations in serum creatinine were added. • Modified the revised Cheson IWG response criteria in order to adapt the criteria to children. • Added definition of relapse after HSCT in children with JMML to the current JMML response criteria. • Removed vaccinations from the list of prohibited medications and added to the list of permitted medications.</p>
12 May 2015	<p>• Clarified IV administration of AZA as preferred route over SC route. • Added rationale for selecting the dose of 75 mg/m<sup>2</sup>. • Amended secondary endpoint of treatment-related AEs to TEAEs. • Added 14-day visit window to Day 1 of Cycles 2 to 6. • Clarified pregnancy testing requirements. Clarified that female and male subjects who reached 18 years while on study must have agreed to undergo physician-approved sex education at specified time points. • Specified the pre-HSCT hematology assessments were to be performed only if &gt; 21 days since the last hematology assessment. • Corrected footnotes in Table of Events related to JMML response categories and corrected timing text of BM aspirates for mutational analysis. • Specified that PEs were to include evaluation for PD for JMML subjects in order to evaluate patients according to current JMML response criteria. • Removed statement related to catheter flushing prior to PK sampling. • Added acceptable deviation windows to PK sampling schedules. • In response to regulatory concerns, the barrier method in combination with spermicide was removed as a contraceptive method. • Specified IV dosing of AZA was required to be completed within 45 minutes instead of 60 minutes. • Specified that AZA was incompatible with 5% dextrose. • Clarified subjects with delayed treatment due to renal toxicity were an exception to starting the 2nd or 3rd cycles of treatment no later than 42 days after Day 1 of the previous cycle since these subjects may require more time for renal function to return to baseline values. • Clarified safety data will not be presented for the historical controls. • Revised text to distinguish treatment discontinuation and study discontinuation. • Clarified amendments were to be submitted to the IEC and regulatory authorities for written approval in accordance with legal requirements. • Improved language regarding compliance with Celgene publication policy and included language regarding public website/registry posting.</p>

06 August 2018	<ul style="list-style-type: none"> <li>• The long-term follow-up was reduced to 1 year from the last dose of IP instead of 2 years as 1 year of information post last dose would allow sufficient time to follow the patients through HSCT and also provided sufficient post HSCT survival and safety information during follow up.</li> <li>• Clarified that as the matched-pairs analysis was not viable due to a lack of key data critical to establish pairing of subject which was central to the analysis, other methodologies were explored to allow evaluation of response rates which were either reported in available literature or identified in patient registry database(s). Further analyses would have looked to compare response rates in subjects who received other therapy(ies) in this disease setting.</li> <li>• Clarified the language on the dilution volume of azacitidine and updated suggested infusion dilution volumes to align with the protocol clarification letter that was provided to sites on 25 Aug 2015.</li> <li>• Updated the title s for the Clinical Research Scientist contacts.</li> </ul>
----------------	---

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.

As fewer than 2 MDS subjects had a response after stage 1, enrollment was closed. For the JMML arm, the threshold of confirmed responses was met with 9 subjects achieving a confirmed clinical response. Hence, Stage 2 was not executed for the JMML arm

Notes: