15 October 2020
EMA/295254/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Vidaza

azacitidine

Procedure no: EMEA/H/C/000978/P46/035

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 6 April 2020, the MAH submitted a completed paediatric study for Vidaza, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that AZA-AML-004 is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

Azacitidine was supplied as a sterile lyophilized powder containing 100 mg of azacitidine and 100 mg of mannitol per vial. This is the same pharmaceutical formulation that is approved for adults in the EU for subcutaneous (SC) administration.

An alternate administration route, IV administration, has been used in this study. Reconstitution for clinical IV administration is conducted at the hospital and is supported by a simplified Investigational Medicinal Product Dossier (IMPD, Version 2.0, dated May 2015) that includes relevant compatibility and in-use stability data.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study AZA-AML-004:** 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 leukaemia in molecular relapse after first complete remission.

2.3.2. Clinical study AZA-AML-004

First subject first visit: 12 Aug 2015

Last subject last visit: 08 Oct 2019

Date of report: 05 Mar 2020

Methods

Objectives

The primary objective of the *Safety Run-in Part* was to establish a safe and tolerable dose of azacitidine to be used in the Randomized Part of the study. The secondary objective of the Safety Run-in Part was to establish azacitidine plasma PK parameters in AML subjects at molecular relapse after CR1 and to assess efficacy.

The primary objective of *the Randomized Part* was to evaluate the effect of azacitidine treatment in AML paediatric subjects at molecular relapse after CR1 when compared to no treatment with regard to the progression-free rate at Day 84 (± 4 days) post randomization. The secondary objective of the Randomized Part was to evaluate the safety, pharmacodynamics, and efficacy of azacitidine treatment in AML subjects at molecular relapse after CR1.

Study design

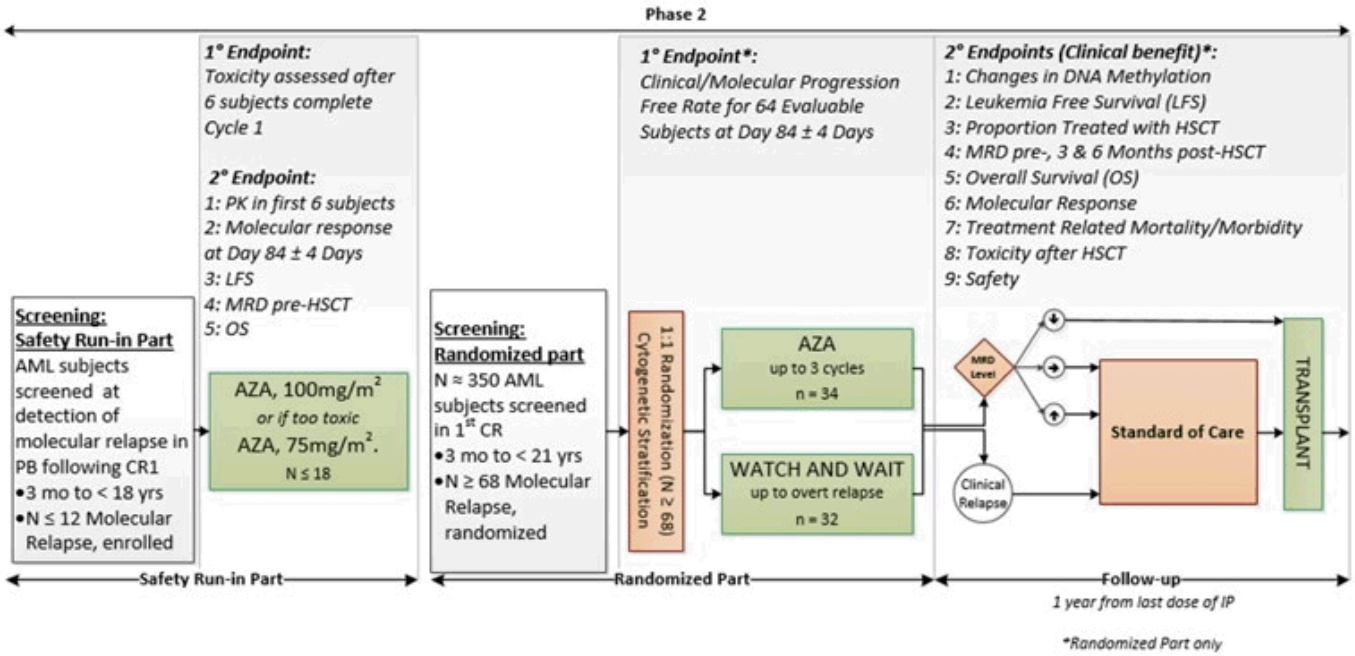


Figure 1 Overall Study Design of Study AZA-AML-004

Study population /Sample size

During the Safety Run-in Part, 6 subjects were to be enrolled in the first cohort of 100 mg/m^2 azacitidine administered intravenously (IV) on Days 1 to 7 of a 28-day cycle. If the 100 mg/m^2 dose was considered unsafe or intolerable, 6 additional subjects were to be enrolled into a 75 mg/m^2 cohort of azacitidine administered IV on Days 1 to 7 of a 28-day cycle. Six further subjects were to be treated in the Safety Run-in Part at the highest tolerated dose to gain preliminary efficacy data before the Randomized Part opened to enrollment.

The Randomized Part was to begin once the Safety Run-in Part was completed and preliminary efficacy established. Subjects who achieved a confirmed molecular CR1 at the start of last consolidation treatment, or within 1 month after completion of consolidation treatment, were to be enrolled into the Randomized Part of the study. The Randomized Part of the study was not conducted. The study was transitioned to a single-arm (N = 20) Phase 2 non-Celgene sponsored study. Therefore, this section only summarizes results for the Safety Run-in Part.

Treatments

Enrolled subjects were to be treated for up to 3 cycles with 100 mg/m^2 azacitidine administered IV on Days 1 to 7 of a 28-day cycle. During any cycle of treatment, subjects who discontinued treatment due

to intolerance of the 100 mg/m2 dose were to have the 28-day Safety Follow-up Visit and then were to enter the Long-term Follow-up Period. These subjects were to be followed by monitoring every 28 days from last dose for MRD level until Day 84 (± 4 days) post Cycle 1 Day 1.

The rate of the following treatment-related DLTs as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03, occurring during Cycle 1 only were to be considered in determining the tolerability of the 100 mg/m^2 dose of azacitidine:

☐ 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 3 or 4 hematologic toxicity requiring treatment delay > 21 days (disease-related Grade 3 or 4 hematologic toxicity was not counted as a DLT)

In general, if a maximum of 1 out of 6 evaluable subjects experienced a treatment-related DLT, as defined above, during Cycle 1, the 100 mg/m^2 dose of azacitidine would have been considered safe for the Randomized Part of the study. If more than 1 out of the 6 evaluable subjects experienced a DLT during Cycle 1, 6 additional subjects were to be enrolled to test the 75 mg/m^2 cohort. If a maximum of 1 out of 6 evaluable subjects experienced a DLT as defined above at the 75 mg/m^2 dose, during Cycle 1, the 75 mg/m^2 dose of azacitidine would have been considered safe for the Randomized Part of the study. If more than 1 of 6 evaluable subjects in the 75 mg/m2 cohort experienced a DLT during Cycle 1, the Randomized Part of the study would not have been initiated

Outcomes/endpoints

The primary endpoint during the **Safety Run-in Part** of the study was:

- Identification of a safe and tolerable dose for the Randomized Part of the study
- Assessment of treatment-related dose-limiting toxicities (DLTs)
- Frequency and severity of treatment-related AEs

The secondary endpoints for the Safety Run-in Part of the study were:

- Molecular response at Day 84 (± 4 days) post Cycle 1 Day 1 (or end of Cycle 3, if not the same date) (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 PB samples and BM aspirates) divided by the number of subjects within the analysis population across time points).
- Azacitidine plasma PK parameters
- Leukaemia-free survival (LFS) (defined as the time from study enrollment until disease progression (identified as clinical progression/clinical relapse, whichever occurred first) or death)
- Minimal residual disease pre-HSCT
- Overall survival (defined as the time from study enrollment until death from any cause).

The primary endpoint during the **Randomized Part** of the study was:

- Progression-free rate at Day 84 (± 4 days) post randomization: Proportion of subjects free from clinical progression (clinical relapse and death from any cause) and from molecular progression (defined as lack of stabilization or lack of decrease in molecular aberrations

concerning FLT3-ITD mutated, CBF leukaemias (eg, t(8;21) and/or inv(16)), MLL-gene rearrangements or NPM1-mutations using central assessment of BM samples by the central laboratories identified for the study, obtained at time points identically prespecified in both randomization arms) at Day 84 (± 4 days) post randomization.

The secondary endpoints for the Randomized Part of the study were:

- Changes in DNA methylation (assessments of BM samples using Nano-HELP assay)
- Leukaemia-free survival
- Proportion treated with HSCT
- Minimal residual disease pre-HSCT, and 3 and 6 months post-HSCT
- Overall survival
- Molecular response
- Treatment-related mortality/morbidity
- Toxicity after HSCT
- Safety

In- and Exclusion criteria

Assessors notes: *only the in-and exclusion criteria for the Safety Run-in Part are depicted as the results from the randomized part were not provided in the CSR. The in-and exclusion criteria necessary for assessment are listed in this AR, please refer to CSR for complete listing.*

Inclusion criteria Safety Run-in

1. Understood and voluntarily provided permission AND able to adhere to the study visit schedule and other protocol requirements

3. Male or female subjects aged 3 months to < 18 years old at the time of informed consent/informed assent

4. Documented diagnosis of AML according to World Health Organization (WHO) classification with at least one of the following molecular aberrations below:

a. t(8;21), RUNX1-RUNX1T1

b. inv(16), CBFb/MYH11

c. t(9;11), MLL-AF9

d. NPM1 mutation

e. FLT3-ITD mutation

5. Documentation of molecular remission (MRD < 5 x 10-4) confirmed at the start of last consolidation course or within 1 month after completion of consolidation treatment

6. Detection of molecular relapse in the PB by RQ-PCR within 7 days prior to signing ICF/IAF and confirmation of molecular relapse during the Screening Period. Molecular relapse was defined as an increase in MRD level of a subject-specific fusion gene or aberration by at least 1 log (10-fold) to a level of at least 5×10^{-4}. Confirmation of a molecular relapse was given if the MRD positivity was at the same level or higher in the PB and BM samples compared to the PB MRD levels at the detection of the

relapse and in the absence of clinical relapse (defined as at least 5% blasts in PB and/or BM and/or proven histological extramedullary relapse)

7. Lansky play score at least equal to 50; or Karnofsky performance status at least equal to 50, whichever was applicable

Exclusion criteria Safety Run-In

Concomitant Treatment

1. Concomitant treatment with any other anticancer therapy except those specified in the protocol

2. Received maintenance therapy after the end of consolidation therapy and CR1

Prior Treatment

3. Hematopoietic stem cell transplantation within previous 3 months

4. Treated by any investigational agent in a clinical study within previous 4 weeks

Medical Condition/Laboratory

5. Pregnant or lactating

6. Symptomatic CNS involvement or isolated extramedullary disease at initial diagnosis

7. French-American-British type M3 leukaemia (APL)

8. Therapy-related AML

9. Acute myeloid leukaemia of Down syndrome or other congenital syndromes giving rise to leukaemia or treatment complications

10. Symptomatic cardiac disorders (NCI CTCAE Version 4.03 Grade 3 or 4)

11. Evidence of invasive fungal infection or other severe systemic infection requiring treatment doses of systemic/parenteral therapy including known active viral infection with human immunodeficiency virus (HIV) or Hepatitis type B and C

12. Any other organ dysfunction (NCI CTCAE Version 4.03 Grade 4) that interfered with the administration of the therapy according to this protocol

13. Acute effects of prior chemotherapy/stem cell transplantation

14. Hypersensitivity to azacitidine

15. Serum bilirubin above 1.5 x upper limit of normal (ULN)

16. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) above 3 x ULN

17. Any significant medical condition including the presence of laboratory abnormalities, which placed the subject at unacceptable risk if he/she were to participate in the study or that would have prevented the subject from participating in the study

Statistical Methods

Primary efficacy evaluation was not applicable for the Safety Run-in Part. All secondary efficacy evaluations were conducted using the ITT Population. Evaluations of the study endpoints were based on point estimates and the associated 95% confidence interval (CI) within treatment doses were to be provided. No formal statistical comparison was to be performed.

There was no formal sample size calculation in the Safety Run-in Part. A total of between 12 and 18 subjects evaluable for determination of the dose for the Randomized Part were required in the Safety Run-in Part. An initial cohort of 6 subjects was to be enrolled and treated at 100 mg/m^2 and if that dose was considered non-tolerable, a further 6 subjects were to be enrolled and treated at 75 mg/m^2. Six further subjects were to be treated in the Safety Run-in Part at the highest tolerated dose to gain preliminary efficacy data before the Randomized Part opened for enrollment.

Results

Recruitment/ Number analysed

The Randomized Part of the study was not conducted. The study was transitioned to a single-arm (N = 20) Phase 2 non-Celgene-sponsored study. Therefore, this CSR presents results for only the Safety Run-in Part.

Per the protocol design, only the 100 mg/m^2 dose was used in this study. No subjects were dosed at 75 mg/m^2.

A total of 7 subjects were screened and no subjects failed screening. Thus, 7 subjects (100.0%) at molecular relapse after CR1 were enrolled in this study and all subjects received the IP.

Table 1 Subject Disposition (Intention-to-Treat Population)

	100 mg/m^2 QD (N = 7) n (%)
Number of Subjects Not Treated	0
Number of Subjects Entered Into Treatment Period	7 (100.0)
Number of Subjects Discontinued From Treatment	2 (28.6)
Number of Subjects Discontinued From Study	2 (28.6)[a]
Number of Subjects Completed	5 (71.4)
Primary Reason for Treatment Discontinuation	
Death	1 (14.3)
Disease Relapse	1 (14.3)
Subjects Discontinued From Study During Treatment Period	
Death	1 (14.3)
Number of Subjects Entered into Long-term Follow-up Period	6 (85.7)
Subject Disposition for the Long-term Follow-up Period	
Discontinued	1 (14.3)
Completed	5 (71.4)
Primary Reason for Study Discontinuation During Long-term Follow-up Period	
Death	1 (14.3)

QD = once daily.
[a] The subject who discontinued from the study during the Follow-up Period is mistakenly presented in Table 14.1.3 as having discontinued from the study during the Treatment Period.
Source: Table 14.1.3.

A total of 6 subjects (85.7%) had at least one protocol deviation during the study. The most common protocol deviation categories were out of window visit or assessment (6 subjects [85.7%]) and procedures or assessments not done (6 subjects [85.7%]). The protocol deviations varied in nature and were not considered to have any clinically relevant impact on data integrity or subject safety.

Baseline data

Demographic and baseline characteristics are summarized in Table 2 for the ITT Population.

Table 2 Demographic and Baseline Characteristics (Intention-to-treat Population)

	100 mg/m^2 QD (N = 7)
Age (years)[a]	
Mean (Standard Deviation)	7.0 (3.78)
Median (Minimum, Maximum)	6.7 (2, 12)
Age Categories (years), n (%)	
< 1	0
≥ 1	7 (100.0)
Sex, n (%)	
Male	5 (71.4)
Female	2 (28.6)
Race, n (%)	
White	7 (100.0)
AML Diagnosis Classification, n (%)[b]	
t(8;21), RUNX1-RUNX1T1	3 (42.9)
inv(16), CBFb/MYH11	4 (57.1)
FLT3-ITD mutation	1 (14.3)[c]
Duration of the Disease (months)[d]	
Median (Minimum, Maximum)	10.320 (9.00, 13.11)

AML = acute myeloid leukemia; BSA = body surface area; QD = once daily.
[a] Age was calculated with one decimal as follows: Age = (date of informed consent/assent – date of birth + 1)/365.25.
[b] A subject was counted more than once if there were several AML diagnoses.
[c] One subject had an FLT3-ITD mutation associated with t(8;21), RUNX1-RUNX1T1.
[d] Duration of disease was expressed in months and was defined as the time from initial AML diagnosis to enrollment.
Source: Table 14.1.5.

All 7 subjects (100.0%) received at least one prior medication. The most frequently used prior medications (in ≥ 2 subjects) were fentanyl (5 subjects [71.4%]), paracetamol and propofol (in 4 subjects [57.1%] each), and remifentanil (2 subjects [28.6%]). No subjects underwent HSCT procedures prior to study enrollment. All subjects received prior systemic anticancer therapies (antineoplastic and immunomodulating agents).

Efficacy results

There were no primary efficacy endpoints defined for the Safety Run-in Part. The secondary efficacy endpoints were analysed based on the ITT Population. At the end of the Safety Run-in Period, the median follow-up time was 14.5 months (14.0 months to 36.0 months), with 5 subjects alive at the time of analysis.

Molecular improvement was seen in 1 subject at Day 84. Three subjects experienced molecular stability on Day 84, and 1 subject had clinical relapse at Day 83.

Four of 7 subjects with minimal residual disease (MRD) assessment at Day 84, had either molecular stabilization (n = 3) or better MRD levels (1 molecular improvement) and 1 subject with MRD assessment on Day 83 had clinical relapse. Overall, the MRD level peaked at Cycle 2 Day 1 in both bone marrow aspirate (BMA) as well as peripheral blood (PB) and then decreased to either baseline level or better.

Six of 7 subjects (90% [95% confidence interval [CI] = 0.4, 1.0]) treated with azacitidine underwent HSCT. One subject died after 2 cycles of treatment and did not undergo HSCT. At the end of the Safety Run-in Period, the median follow-up time was 14.5 months (14.0 months to 36.0 months), with 5 subjects alive at the time of analysis.

The median leukaemia-free survival (LFS) (Intention-to-treat [ITT] Population) was not calculable, as more than 50% of subjects (n = 4) were leukaemia-free at the time of analysis and only 3 subjects either progressed (n = 2) or died (n = 1). The LFS rate was 60% (95% CI = 0.2 to 0.8) at 12 months.

The median OS time was not calculable because more than 50% of subjects were censored at the time of analysis. Five subjects (71.4%) were censored, and 2 subjects (28.6%) died. The OS rate at 12 months and 24 months was 70% (95% CI = 0.3, 0.9).

Table 3 By-subject Summary of Efficacy for Pediatric Acute Myeloid Leukemia Subjects in Study AZA-AML-004 (Intention-to-treat Population)

	MRD Status[a]		
Subject ID	Genetic Aberration	Overall Response	LFS Status
[redacted]	inv(16), CBFb/MYH11	CR	Disease progression
	inv(16), CBFb/MYH11	MS	Alive[b]
	t(8;21), RUNX1-RUNX1T1	MS	Alive[b]
	inv(16), CBFb/MYH11	MI	Alive[b]
	t(8;21), RUNX1-RUNX1T1	NA	Disease progression
	inv(16), CBFb/MYH11	MS	Alive[b]
	t(8;21), RUNX1-RUNX1T1	NA	Death

CR = clinical relapse; HSCT = hematopoietic stem cell transplant; LFS = leukemia-free survival; MI = improvement; MP = molecular progression; MR = molecular response; MRD = minimal residual disease; MS = molecular stabilization; NA = not applicable.
[a] Best response at Day 84 or end of Cycle 3 (by MRD).
[b] Subject received HSCT.
Source: Clinical Study Report AZA-AML-004; Listing 16.2.6.4; Listing 16.2.6.6.1; Listing 16.2.6.6.2.

Pharmacokinetic Results

Pharmacokinetic samples were collected from the first 6 subjects as per protocol on day 7 of the first treatment cycle. All had at least one measurable post-dose PK concentration and were therefore included in the PK Population. Mean azacitidine plasma concentration-time profiles were well characterized over the 6-hour post-dose sampling interval, with all concentrations below the limit of quantification by 6 hours post-dose.

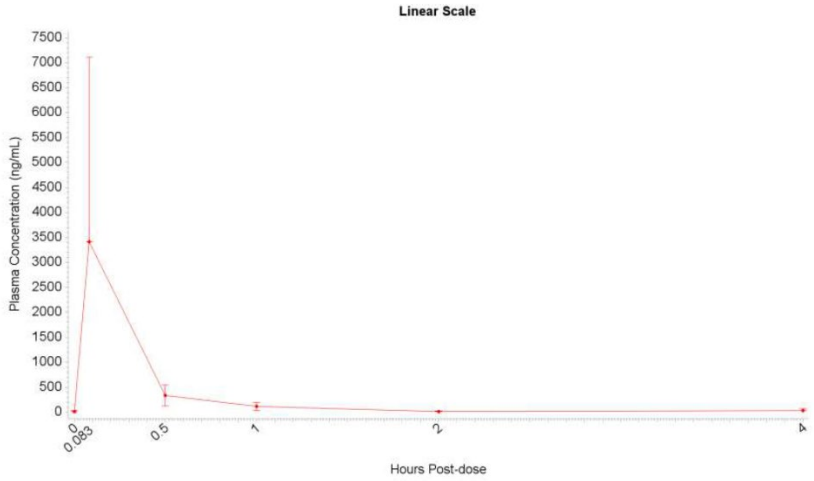
Table 4 and Figure 2 depicts the geometric mean plasma PK parameters following multiple doses of azacitidine 100 mg/m^2 IV.

Table 4 Geometric Mean (Geometric CV%) Plasma PK Parameters of Azacitidine Study AZA-AML-004

AUC_t (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$t_{1/2}$ (h)	CL (L/h)	Vz (L)
N = 6	N = 5	N = 6	N = 6	N = 5	N = 5	N = 5
885.7 (86.3)	787.6 (88.8)	1557 (201.6)	0.090 (0.08-0.53)	0.380 (32.2)	127.2 (73.3)	70.2 (83.7)

$AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time 0 extrapolated to infinity; AUC_t = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; CL = clearance; C_{max} = observed maximum plasma concentration; CV% = coefficient of variation; h = hours; N = number of subjects; PK = pharmacokinetic; $t_{1/2}$ = terminal elimination half-life; T_{max} = observed time to maximum plasma concentration; Vz = volume of distribution.
[a] Median (minimum, maximum).
Source: Table 14.2.7.2.

Figure 2. Mean (+/- SD) Azacitidine Blood Concentrations over Scheduled Time Study AZA-AML-004



According to the Applicant, pharmacokinetic exposure (area under the plasma concentration-time curve from time zero to the last quantifiable time point [AUC0-t]) observed in children and young adults with AML at molecular relapse after CR1 that received 100 mg/m^2 azacitidine are comparable to paediatric subjects included in Study AZA-JMML-001 (10 MDS and 18 JMML subjects) and PK data from 6 adult subjects with MDS administered 75 mg/m^2 azacitidine IV (Study AZA-2002-BA-002) (mean AUC0-t of 1116 ng*hr/ml, 882 ng*hr/ml and 1025 ng*hr/ml, respectively). In addition, azacitidine concentration-time profiles were consistent with previously observed adult and pediatric subjects (JMML and MDS) demonstrating rapid time to peak concentrations, rapid elimination, and high inter-subject variability.

Safety results

For subjects in the study, median treatment duration was 12.00 weeks, with minimum and maximum durations of 8.0 and 13.9 weeks, respectively (Table 5). The median dose intensity of azacitidine was 159.8 mg/m^2/week (range: 142 to 166 mg/m2/week), with a median relative dose intensity of 91.3% (range: 81% to 95%). The majority of subjects (4 subjects [57.1%]) had a relative dose intensity that was $\geq$ 90% and < 100%.

Table 5 Treatment Exposure (Safety Population)

Exposure	100 mg/m^2 QD (N = 7)
Treatment Duration (weeks)[a]	
n	7
Median (Minimum, Maximum)	12.00 (8.0, 13.9)
Treatment Duration Categories (weeks), n (%)	
≥ 3	7 (100)
Number of Cycles	
n	7
Median (Minimum, Maximum)	3.0 (2, 3)
Maximum Number of Treatment Cycles Received, n (%)	
2	2 (28.6)
3	5 (71.4)
Average Cycle Duration (weeks)[b]	
n	7
Median (Minimum, Maximum)	4.48 (4.0, 4.9)
Treatment Duration in Cycle 1 (weeks)	
n	7
Median (Minimum, Maximum)	4.00 (4.0, 5.9)
Treatment Duration in Cycle 2 (weeks)	
n	7
Median (Minimum, Maximum)	4.86 (4.0, 5.9)
Treatment Duration in Cycle 3 (weeks)	
n	5
Median (Minimum, Maximum)	4.00 (4.0, 4.0)

IP = investigational product; QD = once daily.
[a] For subjects who had not completed the last cycle (ie, not all 7 dosing days had been completed in the cycle), treatment duration was defined as [(last day of IP administration) – (Cycle 1 Day 1 of treatment) + 1]/7. For subjects who had completed the last cycle (ie, all 7 dosing days had been completed in the cycle), treatment duration was defined as [(Day 1 of treatment of last cycle + 27) – (Cycle 1 Day 1 of treatment) + 1]/7.
[b] Cycle duration was defined as the time period from Day 1 of each cycle to 1 day prior to Day 1 of subsequent cycle; for the last cycle, end date was the treatment end date.
Source: Table 14.3.1.1.1.

All 7 subjects (100.0%) experienced at least one TEAE and at least one treatment-related TEAE during the study. Serious TEAEs and Grade 3 or higher TEAEs were reported in 3 subjects (42.9%) and 7 subjects (100.0%), respectively. Two subjects (28.6%) experienced a TEAE leading to IP dose interruption. No TEAEs leading to death, IP discontinuation, or IP dose reduction were reported. (Table 6)

Table 6 Overview of Treatment-emergent Adverse Events (Safety Population)

TEAE[a] Categories	100 mg/m^2 QD (N = 7) n (%)
Subjects With at Least One TEAE	7 (100.0)
Subjects With at Least One Grade 3 or Higher TEAE	7 (100.0)
Subjects With at Least One Treatment-related TEAE[b]	7 (100.0)
Subjects With at Least One Treatment-related Grade 3 or Higher TEAE[b]	5 (71.4)
Subjects With at Least One Serious TEAE	3 (42.9)
Subjects With at Least One Treatment-related Serious TEAE[b]	1 (14.3)
Subjects With at Least One TEAE Leading to Death	0
Subjects With at Least One TEAE Leading to IP Discontinuation	0
Subjects With at Least One TEAE Leading to IP Dose Reduction[c]	0
Subjects With at Least One TEAE Leading to IP Dose Interruption[d]	2 (28.6)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; NCI = National Cancer Institute; QD = once daily; TEAE = treatment-emergent adverse event.

[a] Treatment-emergent AEs included AEs that started or worsened between the date of first IP dose and 28 days after the date of last IP dose. Grades were based on NCI CTCAE Version 4.03.

[b] Related = suspected by investigator to be related. Treatment-emergent AEs with a missing relationship were considered as treatment-related TEAEs.

[c] Dose reduction included reduction with or without interruption.

[d] Dose interruption included interruption with or without reduction. There were no subjects who had dose reductions.

Source: Table 14.3.1.2.

A summary of TEAEs by SOC and PT in ≥ 2 subjects is provided in Table 7. The SOCs with the highest proportion (in ≥ 4 subjects) of subjects reporting TEAEs during the study were Blood and Lymphatic System Disorders (7 subjects [100.0%]), Gastrointestinal Disorders (6 subjects [85.7%]), General Disorders and Administration Site Conditions (6 subjects [85.7%]), and Infections and Infestations (4 subjects [57.1%]). The most frequently reported TEAEs (in > 30% of subjects) were neutropenia (7 subjects [100.0%]), nausea (5 subjects [71.4%]), and leukopenia, thrombocytopenia, diarrhoea, and increased ALT (3 subjects [42.9%] each).

Table 7 Treatment-emergent Adverse Events by System Organ Class and Preferred Term in Two or More Subjects (Safety Population)

System Organ Class[a] Preferred Term[a]	100 mg/m^2 QD (N = 7) n (%)
Subjects With at Least One TEAE	7 (100.0)
Blood and Lymphatic System Disorders	7 (100.0)
Neutropenia	7 (100.0)
Leukopenia	3 (42.9)
Thrombocytopenia	3 (42.9)
Febrile neutropenia	2 (28.6)
Gastrointestinal Disorders	6 (85.7)
Nausea	5 (71.4)
Diarrhoea	3 (42.9)
Constipation	2 (28.6)
General Disorders and Administration Site Conditions	6 (85.7)
Fatigue	2 (28.6)
Infections and Infestations	4 (57.1)
Device-related infection	2 (28.6)
Investigations	3 (42.9)
Alanine aminotransferase increased	3 (42.9)
Metabolism and Nutrition Disorders	3 (42.9)
Decreased appetite	2 (28.6)
Nervous System Disorders	2 (28.6)
Headache	2 (28.6)
Respiratory, Thoracic, and Mediastinal Disorders	2 (28.6)
Cough	2 (28.6)

AE = adverse event; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SOC = system organ class; TEAE = treatment-emergent adverse event.
[a] The SOCs and PTs were coded using MedDRA Version 21.0. Adverse events were sorted in descending order of frequency of SOC and PT within SOC. A subject was counted only once for multiple events within PT/SOC.
Note: Treatment-emergent AEs included AEs that started or worsened between the date of first IP dose and 28 days after the date of last IP dose.
Source: Table 14.3.1.3.

Analysis of Adverse Events by Severity

Grade 3 or higher TEAEs by SOC and PT are summarized in Table 8. All 7 subjects (100.0%) experienced at least one Grade 3 or higher TEAE. Neutropenia was the most common Grade 3 or higher TEAE and was reported in 6 subjects (85.7%).

At least 1 treatment-related TEAE was reported in all 7 subjects (100.0%). The most frequently reported treatment-related TEAEs (in ≥ 5 subjects) were nausea and neutropenia (in 5 subjects [71.4%] each)(Table 9).

Table 8 Grade 3 or Higher Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class[a] Preferred Term[a]	100 mg/m^2 QD (N = 7) n (%)
Subjects With at Least One NCI CTCAE Grade 3 or Higher TEAE	7 (100.0)
Blood and Lymphatic System Disorders	6 (85.7)
Neutropenia	6 (85.7)
Febrile neutropenia	2 (28.6)
Leukopenia	1 (14.3)
Infections and Infestations	2 (28.6)
Device-related infection	1 (14.3)
Pneumonia	1 (14.3)
Cardiac Disorders	1 (14.3)
Cardiac failure	1 (14.3)
Investigations	1 (14.3)
Alanine aminotransferase increased	1 (14.3)
Aspartate aminotransferase increased	1 (14.3)
Vascular Disorders	1 (14.3)
Hypotension	1 (14.3)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; PT = preferred term; QD = once daily; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] The SOCs and PTs were coded using MedDRA Version 21.0. Adverse events were sorted in descending order of frequency of SOC and PT within SOC. A subject was counted only once for multiple events within PT/SOC. Grades were based on NCI CTCAE Version 4.03.

Note: Treatment-emergent AEs included AEs that started or worsened between the date of first IP dose and 28 days after the date of last IP dose.

Source: Table 14.3.1.5.

Table 9 Treatment-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term in Two or More Subjects (Safety Population)

System Organ Class[a] Preferred Term[a]	100 mg/m^2 QD (N = 7) n (%)
Subjects With at Least One Treatment-related TEAE[b]	7 (100.0)
Gastrointestinal Disorders	6 (85.7)
Nausea	5 (71.4)
Diarrhoea	2 (28.6)
Blood and Lymphatic System Disorders	5 (71.4)
Neutropenia	5 (71.4)
Leukopenia	2 (28.6)
Thrombocytopenia	2 (28.6)
Investigations	2 (28.6)
Alanine aminotransferase increased	2 (28.6)

AE = adverse event; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] The SOCs and PT were coded using MedDRA Version 21.0. Adverse events were sorted in descending order of frequency of SOC and PT within SOC. A subject was counted only once for multiple events within PT/SOC.

[b] Related = suspected by investigator to be related. Treatment-emergent AEs with a missing relationship were considered as treatment-related TEAEs.

Note: Treatment-emergent AEs included AEs that started or worsened between the date of first IP dose and 28 days after the date of last IP dose.

Source: Table 14.3.1.4.

At least 1 Grade 3 or higher treatment-related TEAE was reported in 5 subjects (71.4%); these TEAEs included neutropenia, febrile neutropenia, leukopenia, pneumonia, alanine aminotransferase increased, and aspartate aminotransferase increased. Neutropenia (4 subjects [57.1%]) was the only Grade 3 or higher treatment-related TEAE reported in ≥ 2 subjects. Grade 3 or higher treatment-related febrile neutropenia, leukopenia, pneumonia, increased ALT, and increased AST were reported in 1 subject (14.3%) each.

Deaths

Two subjects (28.6%) died more than 28 days after the end of treatment. One subject died due to cardiac failure 30 days after the last dose of IP. This subject was an 8-year-old, with a medical history of congenital heart disease pulmonalis atresia (corrected with a fenestrated extracardial Fontan circulation) and surgery to insert cardiac pacemaker (pacemaker placement in June 2016) and received azacitidine treatment. Following administration of Cycle 2, the subject developed febrile neutropenia and pneumonia (treated with antibiotics) followed by Grade 4 hypotension, and heart failure due to deterioration of Fontan circulation. The subject died of heart failure on Study Day 64 (last dose of IP was on Study Day 35). One subject died due to multiple organ dysfunction syndrome 267 days after the last dose of IP.

Other Serious Adverse Events

Three subjects (42.9%) experienced at least one serious TEAE. Febrile neutropenia was the only serious TEAE reported in 2 subjects.

Table 10 Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class[a] Preferred Term[a]	100 mg/m^2 QD (N = 7) n (%)
Subjects With at Least One Serious TEAE	3 (42.9)
Blood and Lymphatic System Disorders	2 (28.6)
Febrile neutropenia	2 (28.6)
Infections and Infestations	2 (28.6)
Device-related infection	1 (14.3)
Pneumonia	1 (14.3)
Cardiac Disorders	1 (14.3)
Cardiac failure	1 (14.3)
Vascular Disorders	1 (14.3)
Hypotension	1 (14.3)

AE = adverse event; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SOC = system organ class; TEAE = treatment-emergent adverse event.
[a] The SOCs and PTs were coded using MedDRA Version 21.0. Adverse events were sorted in descending order of frequency of SOC and PT within SOC. A subject was counted only once for multiple events within PT/SOC.
Note: Treatment-emergent AEs included AEs that started or worsened between the date of first IP dose and 28 days after the date of last IP dose.
Source: Table 14.3.2.1.

Two subjects (28.6%) had at least one TEAE leading to IP interruption. One subject (14.3%) had IP interrupted due to febrile neutropenia and one subject (14.3%) had IP interrupted due to neutropenia.

Treatment-emergent Adverse Events of Special Interest

All 7 subjects (100.0%) experienced at least one AESI. Serious AESIs and Grade 3 or higher AESIs were reported in 3 subjects (42.9%) and 6 subjects (85.7%), respectively. Treatment-related AESIs were reported in 5 subjects (71.4%); 4 subjects (57.1%) experienced at least 1 treatment-related Grade 3 or higher AESI and 1 subject (14.3%) experienced at least 1 treatment-related serious TEAE of special interest. No subjects experienced an AESI leading to IP discontinuation and no subjects experienced a post-HSCT AESI.

The most common AESI categories were myelosuppression and myelosuppression-neutropenia, reported in 7 subjects (100.0%) each (Table 11). There were no reports of AESIs of cardiovascular events or second primary malignancies reported while subjects were receiving IP.

Table 11 Treatment-emergent Adverse Events of Special Interest by AESI Category and Preferred Term in Two or More Subjects (Safety Population)

AESI Category Preferred Term[a]	100 mg/m^2 QD (N = 7) n (%)
Subjects With at Least One TEAE of Special Interest	7 (100.0)
Myelosuppression	7 (100.0)
Neutropenia	7 (100.0)
Leukopenia	3 (42.9)
Febrile neutropenia	2 (28.6)
Myelosuppression-Neutropenia	7 (100.0)
Neutropenia	7 (100.0)
Leukopenia	3 (42.9)
Febrile neutropenia	2 (28.6)
Infections	4 (57.1)
Device-related infection	2 (28.6)
Myelosuppression-Thrombocytopenia	3 (42.9)
Thrombocytopenia	3 (42.9)

AE = adverse event; AESI = adverse event of special interest; HLT = high-level terms; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SMQ = standardized Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] Coded using MedDRA Version 21.0. Adverse events were sorted in descending order of frequency of AESI category and PT within AESI category. A subject was counted only once for multiple events within PT/AESI category.

Note: Treatment-emergent AEs included AEs that started or worsened between the date of first IP dose and 28 days after the date of last IP dose. Categories for TEAE of special interest used either MedDRA Version 21.0 SMQ or sub-SMQ or SOC or HLT or list of PTs. A subject was counted only once for multiple events within preferred term/special interest category. TEAEs were sorted by descending frequency for the overall and PT within AESI category. AESI categories were not exclusive. A subject with the same PT could be counted in more than one category.

Source: Table 14.3.2.8.2.

Laboratory Parameters

The majority of subjects did experience shifts from baseline during treatment for haematology laboratory parameters. These shifts were seen for haemoglobin (anaemia), white blood cell count (WBC decreased), platelet count (platelet count decreased), absolute neutrophils (neutrophil count decreased), absolute lymphocytes (lymphocyte count decreased).

A summary of shift of NCI CTCAE grade from baseline to the worst grade during treatment was observed for Sodium (hypernatremia), Sodium (hyponatremia), Potassium (hypokalaemia), Calcium (hypocalcaemia), Creatinine (creatinine increased), Glucose (hyperglycaemia), Glucose (hypoglycaemia), Albumin (hypoalbuminemia), Alkaline phosphatase (alkaline phosphatase increased), ALT (alanine aminotransferase increased), AST (aspartate aminotransferase increased).

There were no clinically meaningful changes in vital signs, echocardiogram, or performance status during the study.

Conclusion MAH

No conclusions can be drawn with respect to the clinical activity of azacitidine in the paediatric AML population in Study AZA-AML-004 due to the small number of subjects. The study is continuing as a non-Celgene-sponsored study to explore the efficacy in molecular relapse AML. In Study AZA-AML-004, azacitidine administered at the regimen of 100 mg/m^2, IV, QD on Days 1 to 7 of a 28-day cycle was deemed to be the safe and tolerable dose in paediatric subjects with AML. The observed AEs were expected and consistent with the known safety profile for azacitidine. No new safety signals were observed. No subjects required dose modifications and no subjects experienced a treatment-emergent adverse event (TEAE) leading to azacitidine discontinuation or dose reduction.

No conclusions can be drawn with respect to the clinical activity of azacitidine in the paediatric AML population in Study AZA-AML-004 due to the small number of subjects. Due to the limited data available, the MAH does not propose any update to the SmPC with results from this study.

2.3.3. Discussion on clinical aspects

The MAH presents the results from 7 paediatric subjects with a documented molecular relapse treated in the Safety Run-In part of study AZA-AML-004. The Randomized Part of the study was not conducted. The study was transitioned to a single-arm (N = 20) Phase 2 non-Celgene-sponsored study. Therefore, this CSR presents results for only the Safety Run-in Part.

A starting dose of 100 mg/m^2 IV was tested, whereas the recommended dose in the SmPC for adults is 75 mg/m^2 SC, the applicant justified the different dose based on scientific publications and the PK and renal clearance which are higher in children than in adults. The alternate administration route, IV administration (also used in AZA-JMML-001), can be agreed.

A total of 7 subjects, at molecular relapse after CR were enrolled. The majority of these subjects had favourable risk stratification with an AML diagnosis classification of inv(16), CBFb/MYH11 (4 subjects). The majority of subjects were male (5 subjects) and the median age was 6.7 years (range: 2 to 12 years). All subjects received prior systemic anticancer therapies and no subjects underwent HSCT procedures prior to study enrolment. The primary objective for the Safety Run-in Part was establishing a safe and tolerable dose for the Randomized Part of the study, assessment of treatment-related dose-limiting toxicities (DLTs) and determining the frequency and severity of treatment-related AEs. Thus no primary efficacy endpoints were defined. The secondary efficacy endpoints included molecular response at Day 84 or end of Cycle 3 (by MRD), MRD analysis, HSCT rate, LFS, OS and azacitidine plasma PK parameters. Therefore, and due to the lack of the randomized part of the study, the results presented here will only provide limited data on activity of azacitidine in children with AML.

From the 7 enrolled subjects, 2 subjects discontinued treatment (1 due to death (cardiac failure 30 days after the last dose) and the other due to clinical relapse). At day 84, molecular improvement was seen in 1 subject, 3 subjects experienced molecular stability, and 1 subject had clinical relapse at Day 83. The median leukaemia-free survival (LFS) was not calculable, 4 subjects were leukaemia-free at the time of analysis and 3 subjects either progressed (n = 2) or died (n = 1). At the end of the Safety Run-in Period, the median follow-up time was 14.5 months (14.0 months to 36.0 months), with 5 subjects alive at the time of analysis. Six of 7 subjects (90% [95% confidence interval [CI] = 0.4, 1.0]) treated with azacitidine underwent HSCT.

Pharmacokinetic samples were collected from the first 6 subjects as per protocol at day 7 of the first treatment cycle. According to the Applicant, pharmacokinetic exposure (area under the plasma concentration-time curve from time zero to the last quantifiable time point [AUC0-t]) observed in children and young adults with AML at molecular relapse after CR1 that received 100 mg/m^2

azacitidine are comparable to paediatric subjects included in Study AZA-JMML-001 (10 MDS and 18 JMML subjects) and PK data from 6 adult subjects with MDS administered 75 mg/m^2 azacitidine IV (Study AZA□2002-BA-002) (mean AUC0-t of 1116 ng*hr/ml, 882 ng*hr/ml and 1025 ng*hr/ml, respectively). A descriptive analysis showed that mean exposure to azacitidine (Cmax and AUC0-tlast) was similar between both paediatric studies and the adult subjects after IV administration. Similarly, dose-normalized exposure parameters (Cmax/Dose and AUC0-tlast/Dose) pooled across both paediatric studies were comparable to adult dose-normalized parameters.. Further, azacitidine PK data in paediatric patients have been described in SmPC section 5.2, but the final text is not agreed upon yet.

With respect to the safety, all 7 subjects (100.0%) experienced at least one TEAE and at least one treatment-related TEAE during the study. Serious TEAEs and Grade 3 or higher TEAEs were reported in 3 subjects (42.9%) and 7 subjects (100.0%). The most frequently reported TEAEs (in > 30% of subjects) were neutropenia (7 subjects [100.0%]), nausea (5 subjects [71.4%]), and leukopenia, thrombocytopenia, diarrhoea, and increased ALT (3 subjects [42.9%] each). Neutropenia (4 subjects [57.1%]) was the only Grade 3 or higher treatment-related TEAE reported in ≥ 2 subjects. Grade 3 or higher treatment-related febrile neutropenia, leukopenia, pneumonia, increased ALT, and increased AST were reported in 1 subject (14.3%) each. Haematology and serum chemistry parameters were consistent with the known pharmacology of azacitidine and generally worsened from baseline but did not lead to study discontinuation. One subject (14.3%) had IP interrupted due to febrile neutropenia and one subject (14.3%) had IP interrupted due to neutropenia.

Thus, the safety profile in paediatric AML subjects seems consistent with the known safety profile of azacitidine, the most frequently reported TEAEs were primarily hematologic and gastrointestinal disorders. The sample size is too limited to determine whether the frequency of AEs is different from the known safety profile, but there does not seem to be major differences. No new safety signals were observed.

The applicant proposes no changes in the SmPC based on the presented results due to the small number of subjects. Acknowledging the limited studied population, it is considered that the observed activity and safety of azacitidine, as well as azacitidine PK data in (paediatric) patients with AML is of interest to the physicians. This information is provided in the SmPC.

3. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. A starting dose of 100 mg/m^2 was tested, whereas the recommended dose in the SmPC for adults is 75 mg/m^2. In paediatric study AZA-JMML-001 (MDS and JMML) a dose of 75 mg/m^2 was chosen. The reason to decide for a higher starting dose in the AML indication is not understood. The applicant should justify the differences in dosing strategy in AML, MDS and JMML.

2. PK data from the IV route from all paediatric studies should be pooled together with PK data (IV and SC) from adults for an analysis, assessing if the drug exposures from IV administration in paediatrics are comparable with that from SC/IV administration in adults. Such analysis may be conducted using popPK methodology.

3. The MAH is requested to provide a text proposal for the relevant sections of the SmPC (4.2 (no posology recommendation is needed) ,, 4.8., 5.1 and 5.2) describing the results of this study in a concise and informative manner as suggested in the FAQ on SmPC paediatrics information (EMA/551202/2010 Rev 1).

4. As the randomized part of study **AZA-AML-004** has been transferred to a non-Celgene study, the applicant is requested to commit to make every effort to submit any available data from this study (safety part and randomized part) , even when no formal indication in children is sought by the Applicant.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

CHMP QUESTION 1

A starting dose of 100 mg/m2 was tested, whereas the recommended dose in the Summary of Product Characteristics (SmPC) for adults is 75 mg/m2. In paediatric study AZA-JMML-001 (myelodysplastic syndromes [MDS] and juvenile myelomonocytic leukemia [JMML]) a dose of 75 mg/m2 was chosen. The reason to decide for a higher starting dose in the acute myeloid leukemia (AML) indication is not understood. The applicant should justify the differences in dosing strategy in AML, MDS and JMML.

MAH Response

Azacitidine (Vidaza®) has been authorized for treatment in adult patients since 2008 at 75 mg/m2, with some use at 100 mg/m2 in adult AML patients (Khan 2012) and has been widely used in pediatric trials as summarized below. The use of azacitidine at a hypomethylating dose in JMML was reported in a few case studies. A 1.5-year old JMML patient with monosomy 7 was treated with azacitidine 100 mg/m2 in 1-hour intravenous (IV) transfusions for 5 consecutive days of each 28-day cycle for 8 cycles (Furlan, 2009). This dose and regimen of azacitidine resulted in a complete cytogenetic response at the initiation of Cycle 6 and a reduction in methylation of the *CALCA* gene promoter. In pediatric trials, a number of studies specifically designed to evaluate the use of azacitidine to treat AML or acute lymphatic leukemia (ALL) have been published. Azacitidine doses ranging from 50 to 300 mg/m2/day have been used according to pediatric reports (Avramis, 1987; Avramis 1989; Baehner, 1979; Baehner, 1981; Baehner, 1984; Buckley, 1989; Chang, 2000;Dahl, 1990; Gaynon, 1983; Grier, 1992; Hakami, 1985; Hakami, 1987; Hrodek, 1971;Hurwitz,1992; Kalwinsky, 1986; Kalwinsky, 1988; Karon, 1973; Look, 1981; Look, 1982;Ravindranath, 1987; Ravindranath, 1992; Ravindranath, 1993; Ravindranath, 1996;Ribeiro, 1996; Steele, 1988; Steuber, 1989; Steuber, 1991; Steuber, 1994; Steuber, 1996;Sun, 2018; Weinstein, 1983; Woods, 1990; Woods, 1996; Woods, 1996a).

Safety data from these studies accounting for more than 2,200 pediatric patients has adequately characterized the safety of azacitidine alone and in combination with other agents in the pediatric population (Appendix 1, RSI doc MAH). In all these studies, azacitidine was administered as IV, most often in combination with other agents and there were no safety concerns reported at these doses. Because the doses of azacitidine used in the previous pediatric studies likely exceeded the hypomethylating exposure and because azacitidine was given concurrently with combination agents, single-agent azacitidine at 75 mg/m^2 and 100 mg/m^2 was considered in the safety run-in part of the AZA-AML-004 study.

In both pediatric studies (AZA-AML-004 and AZA-JMML-001) the aim was to use the hypomethylating dose (75 mg/m^2 and 100 mg/m^2) based on the published data. For MDS and JMML subjects (AZA-JMML-001), Celgene used 75 mg/m^2 taking into consideration known hematological toxicities of azacitidine, which usually occur during the early course of treatment, while aiming for patients to complete at least 3 cycles before bridging to transplant. For AML patients with molecular relapse after first complete remission (CR1) (AZA-AML-004), as the aim was to lower tumor burden as much as possible before transplant, 100 mg/m^2 was selected as the dose to be tested first in the safety run-in part. If this higher dose was deemed not tolerable, then the study would have assessed the lower dose

of 75 mg/m^2. Based on the above mentioned available literature from the 2,200 pediatric patients, the starting dose of 100 mg/m^2 for study AZA-AML-004 was discussed with the Paediatric Committee (PDCO) and agreed as part of the Vidaza paediatric investigational plan (PIP) (EMEA-001272- PIP02-13-M01, approved 21 Feb 2014).

Assessors comment

Issue has been clarified. No recommendation for posology is made due to the small sample size.

Conclusion

resolved

CHMP QUESTION 2

Pharmacokinetic (PK) data from the IV route from all paediatric studies should be pooled together with PK data (IV and subcutaneous [SC]) from adults for an analysis, assessing if the drug exposures from IV administration in paediatrics are comparable with that from SC/IV administration in adults. Such analysis may be conducted using popPK methodology.

MAH Response to CHMP Question 2

Study AZA-2002-BA-002 was a randomized, open-label, two-period, crossover study to assess the bioavailability of SC and IV azacitidine administered at 75 mg/m^2 in adult subjects with MDS. An 89% bioavailability of SC versus IV route was observed, therefore area under the plasma concentration time curve (AUC) is similar between IV and SC administration in adult subjects (refer to Table 1).

Tabel 1 Summary of Arithmetic Mean (±Standard Deviation) Pharmacokinetic Parameters Following SC and IV Dose Administration (N = 6) in Adults

Route	C_{max} (ng/mL)	$AUC_{0-\infty}$ (h·ng/mL)	AUC_{0-t} (h·ng/mL)	$t_{½}$ (h)	CL (L/h)	V_z (L)
SC	750.0 (403.3)	960.53 (458.06)	923.88 (473.61)	0.69 (0.14)	167.48 (48.69)	
IV	2750.0 (1069.0)	1044.26 (285.67)	1025.11 (298.06)	0.36 (0.02)	146.70 (46.91)	76.076 (25.5)

AUC_{0-t} = area under the plasma concentration time curve from time zero to last time with detectable levels; $AUC_{0-\infty}$ = area under the plasma concentration time curve from time zero extrapolated to infinity; C_{max} = maximum observed plasma concentration; CL = total plasma clearance; IV = intravenous; SC = subcutaneous; $t_{½}$ = half-life in terminal phase; V_z = volume of distribution.
Source: Clinical Study Report AZA- 2002-BA-002.

PK data from pediatric subjects included in Study AZA-AML-004 (6 subjects) treated via IV administration of azacitidine 100 mg/m^2, Study AZA-JMML-001 (10 MDS and 18 JMML subjects) treated via IV administration of azacitidine 75 mg/m^2 and the 6 adult subjects with MDS administered 75 mg/m^2 azacitidine IV in Study AZA-2002-BA-002 are presented in Table 2. In addition, to assess if azacitidine drug exposures from IV administration across pediatric studies are comparable to IV administration in adults, dose-normalized pediatric exposure parameters were pooled and compared to dose-normalized adult exposure parameters. Exposure of azacitidine (maximum observed plasma concentration [Cmax] and AUC from time zero to last time with detectable levels [AUC0-t]) was similar between both pediatric studies and the adult subjects after IV administration. Similarly, dose-normalized exposure parameters (Cmax/Dose and AUC0-t/Dose) pooled across pediatric studies were comparable to adult dose-normalized parameters.

Table 2 Mean (Standard Deviation) of Azacitidine Plasma Pharmacokinetic Parameters in Pediatric and Adult Subjects after IV administration

Azacitidine Parameter	C_{max} (ng/mL)	AUC_{0-t} (h·ng/mL)	$AUC_{0-\infty}$ (h·ng/mL)	$t_{½}$ (h)	CL (L/h)	V_z (L)	C_{max}/Dose (ng/mL/mg/m^2)	AUC_{0-t}/Dose (h·ng/mL/mg/m^2)
Pediatric (AML)[c] (N = 6)	2882 (3551)	1116 (819.4)	1016[a] (872.7)	0.396[a] (0.139)	148.3[a] (82.8)	84.6[a] (51.2)	36.29 (56.56)	11.65 (17.43)
Pediatric (MDS +JMML) (N = 28)[d]	2841 (4537)	882.1 (1421)	700.7[b] (1215)	0.379[b] (0.196)	192.9[b] (178.4)	102.0[b] (91.8)		
Adults (MDS) (N = 6)[d]	2750 (1069)	1025 (298.1)	1044 (285.7)	0.36 (0.02)	146.7 (46.9)	76.1 (25.5)	36.67 (14.25)	13.67 (3.97)

AML = acute myeloid leukemia; AUC_{0-t} = area under the plasma concentration time curve from time zero to last time with detectable levels; AUC_{0-t}/Dose = dose-normalized AUC_{0-t} (area under the plasma concentration time curve from time zero to last time with detectable levels divided by dose); $AUC_{0-\infty}$ = area under the plasma concentration time curve from time zero extrapolated to infinity; C_{max} = maximum observed plasma concentration; C_{max}/Dose = dose-normalized C_{max} (maximum observed plasma concentration divided by dose) ; CL = total plasma clearance; JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome; $t_{½}$ = half-life in terminal phase; V_z = volume of distribution

[a] N = 5

[b] N = 26

[c] 100 mg/m^2 dose administered

[d] 75 mg/m^2 dose administered

Sources: Clinical Study Report AZA-AML-004; Clinical Study Report AZA-JMML-001; Clinical Study Report AZA-2002-BA-002.

Assessors comment

The Applicant did not pool the PK data from the IV route from all paediatric studies together with the PK data (IV and subcutaneous [SC]) from adults, either via additional grouping and descriptive statistics nor via popPK analysis. Only data from two paediatric studies were pooled. Instead, the Applicant displayed additional tables with descriptive statistics of the various paediatric and adult groups studied, to assess if the drug exposures from IV administration in paediatrics are comparable with that from SC/IV administration in adults.

The tables above show that mean exposure to azacitidine (C_{max} and $AUC_{0-tlast}$) was similar between both pediatric studies and the adult subjects after IV administration. Similarly, dose-normalized exposure parameters (C_{max}/Dose and $AUC_{0-tlast}$/Dose) pooled across both paediatric studies were comparable to adult dose-normalized parameters.

Conclusion

Issue resolved.

CHMP QUESTION 3

The MAH is requested to provide a text proposal for the relevant sections of the SmPC (4.2 [(no posology recommendation is needed]), 4.8., 5.1 and 5.2) describing the results of this study in a concise and informative manner as suggested in the FAQ on SmPC paediatrics information (EMA/551202/2010 Rev 1).

MAH Response

As requested, the MAH is submitting herein a draft Vidaza Summary of Product Characteristics (SmPC) document in track changes, including proposed updates to Sections 4.2, 4.8, 5.1, and 5.2. The new proposed text is shown in underline below, and proposed deleted text in strikethrough.

- SmPC Section 4.2

The safety and efficacy of Vidaza in children aged 0-17 years have not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on posology can be made. ~~No data are available.~~

- SmPC Section 4.8

Paediatric population

In Study AZA-AML-004, 7 paediatric patients (aged 3 months to less than 18 years) were treated with Vidaza for AML in molecular relapse after first complete remission [CR1] (see section 5.1).

All 7 patients experienced at least 1 treatment-related adverse event. The most frequently reported adverse events were neutropenia, nausea, leukopenia, thrombocytopenia, diarrhoea and increased alanine aminotransferase (ALT). Two patients reported a treatment-related adverse event which led to dose interruption (febrile neutropenia, neutropenia).

No new safety signals were identified in the limited number of paediatric patients treated with Vidaza during the course of the clinical study. The overall safety profile was consistent with that of the adult population.

- SmPC Section 5.1

Paediatric population

Study AZA-AML-004 was a Phase 2, multicentre, open-label study to evaluate the safety, pharmacodynamics and efficacy of Vidaza compared to no anti-cancer treatment in children and young adults with AML in molecular relapse after CR1.

Seven patients (median age 6.7 years [range 2 to 12 years]; 71.4% male) were treated with intravenous Vidaza 100 mg/m2, daily on Days 1 to 7 of each 28-day cycle for a maximum of 3 cycles.

Five patients had minimal residual disease (MRD) assessment at Day 84 with 4 patients achieving either molecular stabilization (n = 3) or molecular improvement (n = 1) and 1 patient

had clinical relapse. Six of 7 patients (90% [95% CI = 0.4, 1.0]) treated with azacitidine underwent haematopoietic stem cell transplantation (HSCT).

Because of the small patient number, the efficacy of Vidaza in paediatric AML cannot be established.

See section 4.8 for safety information.

- SmPC Section 5.2

Paediatric population

In Study AZA-AML-004, pharmacokinetic analysis was determined from 6 of the 7 paediatric patients, which had at least one measurable postdose pharmacokinetic concentration (see section 5.1). The median age (range) of the AML patients was 6.7 (2-12) years.

Following multiple doses of 100 mg/m2, the geometric means Cmax and AUC0-∞ on Cycle 1 Day 7 were 1557 ng/mL and 787.6 ng·h/mL, respectively, with high inter-subject variability (CV% of 201.6% and 88.8%, respectively) observed. Azacitidine rapidly reached Cmax, with a median time of 0.090 hours post-intravenous administration and declined with a geometric mean t1/2 of 0.380 hours. The geometric means for clearance and volume of distribution were 127.2 L/h and 70.2 L, respectively.

Pharmacokinetic exposure observed in children with AML at molecular relapse after CR1 are comparable to paediatric patients included in Study AZA-JMML-001 and to adult patients with MDS in Study AZA-2002-BA-002.

Assessors comment

Text proposals for section 4.2., 4.8 and 5.1 are agreed.

The text proposal for Section 5.2 is for the most agreed, except that exposure to azacitidine after multiple dosing should be described by $AUC_{0\text{-}tau}$ instead of $AUC_{0\text{-}\infty}$.

Furthermore the last sentence referring to two other studies is not clear, as those studies are not mentioned in the SmPC (i.e. in Section 5.1).

The proposal should be adapted.

For the last sentence the following wording is proposed: Pharmacokinetic (azacitidine) exposure in children with AML at molecular relapse after CR1 was comparable to exposure from pooled data of 10 children with MDS and 18 children with JMML and also comparable to azacitidine exposure in adults with MDS.

Furthermore, please write MDS and JMML full-out or explain abbreviations.

Conclusion

Issue partly agreed. The proposal for SmPC should be adapted according to the above advice, please refer to the SmPC with Rapporteur's comments included.

CHMP QUESTION 4

As the randomized part of study AZA-AML-004 has been transferred to a non-Celgene study, the applicant is requested to commit to make every effort to submit any available data from this study (safety part and randomized part), even when no formal indication in children is sought by the Applicant

MAH Response

Celgene acknowledges the CHMP's comment and would like to emphasize that data collection and analysis of the two study parts are performed by two different entities/sponsors. The results of the safety run-in part of AZA-AML-004 were presented as part of this submission. The MAH commits to make every effort to submit the clinical study report of the non-Celgene study (VZ-CL-AML-GPOH-13094, EudraCT: 2017-003422-32), despite Celgene not being the sponsor of that clinical trial and having limited influence and rights over the resulting data. Hence, the submission of data from the non-Celgene study can only occur within one year after study completion, which is currently estimated for 2022.

Assessors comment

All efforts of the MAH to provide data from study AZA-AML-004 are welcomed.

Conclusion

Issue not further pursued

4. CHMP overall conclusion and recommendation

The benefit-risk balance for the studied populations cannot be determined due to the limited efficacy data presented. No new safety signals have been identified and the disease targeted is an approved indication of azacitidine. Therefore it is considered that the results of this study do not impact the benefit-risk of azacitidine in the already approved (adult) indications.

Nevertheless, the safety data obtained in the current study are considered of interest to the physicians treating children with AML. Therefore the SmPC should be updated accordingly. A variation including the agreed changes (see Attachment 1) should be submitted within 60 days of the outcome of this P46 procedure.

The benefit-risk for the approved indications remains favourable.

x Fulfilled