Amsterdam, 23 July 2020
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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/P46/034.1

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 25 November 2019 the MAH submitted a completed paediatric study for Vidaza (azacitidine), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

In addition to the study report a short critical expert overview has been provided. The cover letter stated that the MAH is currently assessing whether to submit a subsequent type II variation to update the SmPC (sections 5.1, 5.2 and 4.8) with information from the JMML arm of this study.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the Phase 2, multicentre, open-label study to evaluate the pharmacokinetics, pharmacodynamics, safety and activity of azacitidine and to compare azacitidine to historical controls in paediatric subjects with newly diagnosed advanced myelodysplastic syndrome or juvenile myelomonocytic leukaemia before hematopoietic stem cell transplantation, AZA-JMM-001 is a stand-alone 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 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

Vidaza (azacitidine, EU/H/C/000978) is approved in the European Union (EU) since 17 December 2008 as a powder for suspension for injection for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPPS),
- chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification,
- AML with >30% marrow blasts according to the WHO classification.

Vidaza (azacitidine) does not fall under requirements of Article 8 of the Paediatric Regulation, Regulation (EC) No 1901/2006, as amended.

A voluntary Paediatric Investigational Plan (PIP) was approved by the European Medicines Agency (EMA) on 21 February 2014 (EMEA-001272-PIP02-13, Decision P/0031/2014) including two clinical studies:

- AZA-AML-004, Phase 2 study in children and young adults with AML in molecular relapse after first complete remission
- AZA-JMML-001, Phase 2 study in paediatric subjects with newly diagnosed advanced MDS or JMML before HSCT

The PIP was modified once with modification EMEA-001272-PIP02-13-M01 approved on 02 October 2015. On 19 June 2017, the Marketing Authorisation Holder (MAH) notified EMA of the discontinuation of the PIP for commercial reasons.

This procedure concerns the submission of the final results of study AZA-JMML-001 involving paediatric patients in accordance with Article 46 of the paediatric regulation.

2.3.2. Clinical study

Clinical study number and title

Study AZA-JMML-001: 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 paediatric subjects with newly diagnosed advanced myelodysplastic syndrome or juvenile myelomonocytic leukaemia before haematopoietic stem cell transplantation.

Description

Study AZA-JMML-001 was an international, multicenter, open-label, Phase 2 study designed to evaluate the efficacy and safety of azacitidine as monotherapy for the treatment of paediatric subjects with newly diagnosed advanced myelodysplastic syndromes (MDS) and juvenile myelomonocytic leukaemia (JMML) before haematopoietic stem cell transplantation (HSCT).

Subjects were treated with azacitidine 75 mg/m^2 (IV or SC), QD on Days 1 to 7 of a 28-day cycle for a minimum of 3 cycles and a maximum of 6 cycles. The aim of treatment was to reduce the disease burden with minimal toxicity in order to improve efficacy of stem cell transplantation and thus overall survival (OS). The primary objective of the study was to evaluate the effect of azacitidine on confirmed response rate at Cycle 3 Day 28, and to compare against standard therapy using a matched-pairs analysis with historical data.

CHMP comment

Note that all patients were expected/intended to proceed to haematopoietic stem cell transplantation (HSCT) following azacitidine treatment during the follow up period (at least 28 days after last azacitidine treatment).

No information on recommended or used HSCT procedure (e.g. conditioning regimen, stem cell donor) seem to be provided in the protocol or study report.

Methods

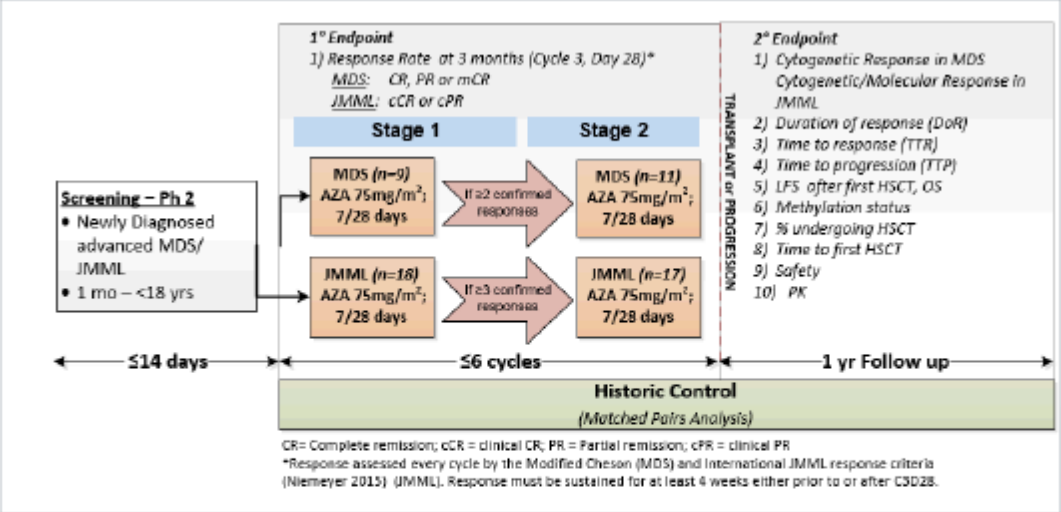
Objective(s)

The primary objective is to assess the treatment effect on response rate (MDS: CR, partial response [PR], or marrow CR; JMML: either cCR or cPR) at Cycle 3 Day 28 and to compare against standard therapy using a matched-pairs analysis with historical data.

Secondary objectives are to further evaluate safety, efficacy, pharmacodynamics (PD), and pharmacokinetics (PK) of azacitidine in this subject population.

Study design

This was a prospective, open-label, Phase 2 study designed to evaluate the efficacy, PD, PK, and safety of azacitidine administered in paediatric subjects enrolled in 2 parallel experimental arms, one for each disease indication: newly diagnosed advanced MDS and newly diagnosed JMML (see Figure 1).



AZA = azacitidine; CR = complete remission; cCR = clinical complete remission; cPR = clinical partial remission; HSCT = hematopoietic stem cell transplantation; JMML = juvenile myelomonocytic leukemia; LFS = leukemia-free survival; mCR = marrow complete remission; MDS = myelodysplastic syndrome; OS = overall survival; Ph2 = Phase 2; PK = pharmacokinetics; and PR = partial response.
Note: MDS subjects are not discussed in this Clinical Overview.
Source: Clinical Study Report AZA-JMML-001, Figure 1.

Figure 1 Overall study design of study AZA-JMML-001

Study population /Sample size

The study will enrol paediatric children aged 1 month to less than 18 years with newly diagnosed advanced MDS or JMML.

For MDS, diagnosis was to be confirmed within 14 days prior signature as refractive anaemia with excess blasts (REAB) (2-19% blast in PB or 5-19% blast in BM), REAB-t (20-29% blast in PB or BM), or secondary MDS presenting as CMML without increase in blasts but with chromosomal abnormality.

For JMML, diagnosis was to be confirmed within 14 days prior signature with a somatic mutation in PTPN11, KRAS, or NRAS and HbF % > 5x normal value for age, or by clinical diagnosis of neurofibromatosis type 1 or NF-1 mutation. Subjects were required to have splenomegaly and less than 20% blast in PB and BM. Subjects with germline molecular aberrations in CBL, PTPN11, NRAS, or KRAS were excluded.

Each arm was designed based on Simon's Optimal 2-stage study design. The sample size was calculated to allow evaluation of the confirmed response rate after 3 cycles of treatment in each of the 2 disease indications. Twenty subjects with MDS and 35 JMML subjects evaluable for the primary endpoint (i.e., subjects that received at least 1 dose of IP) were to be enrolled at approximately 45 centers in Europe. If, during Stage 1 evaluation, less than 2 subjects are observed with CR, PR or marrow CR after 3 cycles of azacitidine in the first 9 subjects with MDS then enrollment will be stopped. Similarly, if less than 3 subjects are observed with cPR or cCR after 3 cycles of azacitidine in the first 18 subjects with JMML, then enrollment will be stopped.

Treatments

Subjects were to be treated with azacitidine, 75 mg/m^2, IV or SC, QD on Days 1 to 7 of a 28-day cycle for a minimum of 3 cycles and a maximum of 6 cycles, provided that the subject does not have disease progression (based on an independent central review of responses). Intravenous administration was the preferred route. The SC route of administration was only to be used in situations where it was not clinically possible to administer azacitidine through IV (e.g., central venous line complications, etc).

All supportive care was permitted.

CHMP comments:

The azacitidine dose of 75 mg/m^2 was chosen in order to provide efficacy but minimal toxicity in both the MDS and JMML patient populations. This is the same starting dose as recommended for the approved (adult) indication. This starting dose was agreed upon with the PDCO.

While not specified in the description of study treatment, all patients were expected to proceed to haematopoietic stem cell transplantation (HSCT) following azacitidine treatment, irrespective of the treatment effect of azacitidine. Which is supported as HSCT is the only curative treatment option for patients with AML and JMML. However, this significantly hampers the interpretability of the clinical relevance of a treatment effect. While an anti-tumour effect may be noted in terms of reduction in disease burden, the added value thereof on clinically relevant outcome measures such as OS or LFS cannot be estimated as this is confounded by HSCT, and while it is intuitively appealing to assume that a reduced tumour burden will increase the curative success of HSCT, this has currently not been shown for (paediatric) patients wilt AML or JMML.

Importantly, as a control arm is lacking in the study design and thus the interpretation of the potential effect of azacitidine treatment prior to HSCT on OS or LFS need to rely on extrapolation form adults (for AML only, JMML is a childhood disease) and/or on cross study comparisons.

To contextualise the results, a comparison with a historical control group collected from the EWOG-MDS registry by means of a matched-pairs analysis was envisaged in the study protocol.

All subjects received azacitidine from Cycles 1 through 3; however, if by the beginning of Cycle 3, the conditions below are met, the subject could receive up to 3 additional cycles (Cycles 4 through 6) of IP 75 mg/m2 QD, IV or SC, for 7 days of a 28-day cycle, at the investigator's discretion:

- an MDS subject was in PR, CR, or marrow CR based on central review of responses as determined by the independent external expert or
- a JMML subject was in cCR or cPR based on central review of responses as determined by the independent external expert.

For MDS or JMML subjects who did not meet the above criteria by the beginning of Cycle 3, the decision regarding the additional 3 cycles of treatment was to be based on central review of the Cycle 3 Day 28 assessments.

If central review by the independent external expert determined that an MDS or JMML subject had stable disease or disease progression at the Cycle 3 Day 28 visit, the subject was to be discontinued and treated as per the institution's standard of care. If at any point during Cycles 4 through 6 a subject experienced disease progression, as per the central review, the subject was to be discontinued.

Outcomes/endpoints

The primary endpoint was the response rate at Cycle 3 Day 28, defined as:

- MDS: Proportion of subjects with CR, PR, or marrow CR according to modified IWG Response criteria (based on Table 3 in Cheson, 2006), adapted to paediatric reference values at 3 months (Cycle 3, Day 28). Response must have been sustained for at least 4 weeks either in the 4-week period preceding or succeeding Cycle 3 Day 28 (ie, sustained over the period Cycle 2 Day 28 to Cycle 3 Day 28, or Cycle 3 Day 28 to Cycle 4 Day 28).
- JMML: Proportion of subjects with sustained cCR or cPR according to the International JMML response criteria in Niemeyer 2015 at 3 months (Cycle 3 Day 28). Response must have been sustained for at least 4 weeks either in the 4-week period preceding or succeeding Cycle 3 Day 28 (i.e., sustained over the period Cycle 2 Day 28 to Cycle 3 Day 28, or Cycle 3 Day 28 to Cycle 4 Day 28).

Furthermore, as a sensitivity analysis for the primary endpoint in the JMML cohort, the response assessment at Cycle 3 Day 28 will be assessed according to the updated response assessment criteria (Niemeyer, 2018).

Secondary endpoints were

- Cytogenetic response for MDS subjects; cytogenetic and molecular response for JMML subjects
- Duration of response (DoR)
- Time to response (TTR)
- Time to progression (TTP)
- Leukaemia-free survival (LFS)
- Overall survival (OS)
- Deoxyribonucleic acid methylation status in BM on Days 1 and 15 of Cycle 1, Day 28 of Cycle 3, pre-HSCT, and at the time of relapse/progression
- Percentage of subjects undergoing HSCT
- Time to first HSCT
- Safety defined by frequency and severity of treatment-emergent AEs (TEAEs)
- Pharmacokinetics. (Sampling was to be done for all subjects on Days 5, 6, and 7 of Cycle 1.

The Primary and Safety Population (defined as all subjects who received at least 1 dose of azacitidine) was used for analysis of the primary endpoint for each disease indication as well as all safety endpoints.

The Intention-to-treat (ITT) Population, defined as all subjects enrolled into the study regardless of whether or not they received any dose of azacitidine, was used for the analysis of all efficacy-based secondary endpoints and for listings.

The PK population consisted of all subjects who received at least 1 dose of azacitidine and had at least 1 measurable concentration of azacitidine. In patients weighing ≤20 kg, blood samples were taken ≤1

hour prior to dosing in cycle 1 day 5, and cycle 1 day 6, as well as 5 (in case of IV only), 15 (in case of SC only), 30 min, 1, 4 and 6 hours post-dose at day 7. In patients weighing >20 kg, and pre-dose and at 5 (in case of IV only), 15 (in case of SC only), 30 min, 1, 2, 4 and 6 hours post-dose at day 7.

CHMP comment:

The primary endpoint is suitable to the aim of treatment, i.e. to establish preliminary activity of azacitidine in subjects with either newly diagnosed advanced MDS or JMML. Indeed response rates are informative regarding the activity of azacitidine against MDS and JMML, however, as noted above, the clinical relevance of such a response is difficult to estimate as subjects were expected to proceed to HSCT (irrespective of a response to azacitidine treatment).

Statistical Methods

Each experimental arm is independent of the other and will run in parallel to each other. Each experimental arm employs Simon's 2-stage design to assess the response rate (CR, PR or marrow CR [MDS] and cCR or cPR [JMML]), at Cycle 3 Day 28. Each arm will then be compared to a historical control arm in a matched-pairs analysis using historical data retrospectively collected from the EWOG registry.

- Advanced MDS subjects will be matched (1:1) by BM blast count (5% to 19%, 20% to 29%), and type of MDS (primary MDS, secondary MDS). Whether a meaningful matched-pair analysis can be completed will depend in part on the characteristics of MDS subjects included in the study.
- Each JMML subject in the study will be matched with 2 subjects (1:2, experimental:control). Pairs will be matched for the clinical risk factors age (< 2 years, $\geq$ 2 years) and platelet count (< 40,000 and $\geq$ 40,000/μL) at the time of diagnosis. These risk factors were chosen based on previous report (Niemeyer, 1997). HbF, another known risk factor, will not be utilized since it is dependent on karyotype and, at least in some studies, also on age. In JMML, there is currently no evidence that karyotype (normal versus monosomy 7) or mutational subtype (NF-1, somatic mutations in PTPN11, NRAS or KRAS) have prognostic value.

Specific disease indication historical control data will not be collected nor considered for analysis if the related experimental arm does not continue past Stage 1 (the interim analysis).

For MDS a lower and upper boundaries of interest in the response rate (CR, PR, or marrow CR) were 10% and 40% respectively. For JMML the lower and upper boundaries of interest in response rate (cCR or cPR) were 10 and 30%.

Results

Recruitment/ Number analysed

As of the cut-off date of 13 Mar 2019, a total of 34 subjects (12 in the MDS arm and 22 in the JMML arm) had been screened and 6 subjects (2 in the MDS arm and 4 in the JMML arm) had failed screening (see Table 1), mainly due to not meeting inclusion criteria. Overall, 28 subjects were enrolled by 18 activated investigational sites from 10 European countries (Czech Republic, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, and Switzerland).

Table 1 Subject disposition (ITT)

	MDS Subjects (N = 10) n (%)	JMML Subjects (N = 18) n (%)
Subjects Entered the Treatment Period	10 (100)	18 (100)
Subjects Completed the Treatment Period	7 (70.0)	15 (83.3)
Subjects Discontinued from the Treatment Period	3 (30.0)	3 (16.7)
Reason for Treatment Discontinuation During the Treatment Period		
Adverse Event	1 (10.0)	1 (5.6)
Progressive Disease	0	2 (11.1)
Physician Decision	2 (20.0)	0

JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome.
Source: Table 14.1.3.1.

Data analyses

Each experimental arm had one interim analysis for futility planned (at the end of Stage 1).

For the MDS experimental arm, the interim analysis was conducted once the first 9 subjects eligible for the primary analysis had completed Cycle 3 Day 28. As fewer than 2 subjects had a response (either CR, PR, or marrow CR) at the time of the interim analysis, the MDS arm was closed to enrollment after Stage 1 completion. Note: 10 subjects were enrolled as the tenth subject was screened prior to the decision being made.

For the JMML experimental arm, the interim analysis was conducted once the first 18 subjects eligible for the primary analysis had completed Cycle 3 Day 28. The JMML arm was closed to enrollment after Stage 1 completion due to the threshold for confirmed response for the whole study (Stage 1 plus Stage 2) (i.e., 7 of 35 responders) being met in Stage 1 alone with 9 subjects achieving a confirmed clinical response.

At the time of DCO (17 Mar 2019) 17 subjects (9 in the MDS arm, 8 in the JMML arm) completed the Follow-up Period, and 8 JMML subjects were still continuing in the Follow-up Period. Overall, 3 subjects (1 in the MDS arm, 2 in the JMML arm) discontinued the study due to death.

CHMP comment:

It is noted that for both study arms enrolment was closed after stage 1 of the study; for MDS enrolment was closed due to lack of success, while for JMML enrolment was closed because the criterion for success (i.e. the threshold for confirmed response) was already met after Stage 1.

Study conduct

The original protocol (dated 11 Sep 2014) was amended 3 times (18 Dec 2014, 13 May 2015 and 07 Aug 2018. The first two amendments are dated prior to first subject first visit (03 Sep 2015). With the third protocol amendment the long-term follow-up was reduced to 1 year from the last dose of azacitidine instead of 2 years. With this amendment it was also 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).

For the MDS and JMML arms, 10 subjects (100%) and 17 subjects (94.4%), respectively, had at least 1 protocol deviation during the study, and 8 subjects (80.0%) and 8 subjects (44.4%) for the MDS and JMML arms, respectively, had at least 1 protocol violation. The most common protocol deviation

categories were "procedures or assessments not done", the most common protocol violation categories were "IP issues" (e.g. timing of administration, dose calculation, given outside of window of 45 minutes following reconstitution).

The protocol deviations and violations were not considered to have any clinically relevant impact on data integrity or subject safety by the Sponsor.

CHMP comment

While the number of protocol deviations/violations seems rather high, it is agreed that the impact of these deviations/violations on subject safety is limited. In case this study would be used for an extension of indication, clarification on the number of protocol deviations/violations should be provided.

Baseline data

Demographic and baseline (disease) characteristics are summarized in Table 2 and Table 3.

Table 2 Demographic and Baseline Characteristics (ITT)

Population	MDS Subjects (N = 10)	JMML Subjects (N = 18)
Age (years)[a], n	10	18
Mean (Standard Deviation)	11.16 (4.862)	2.38 (1.685)
Median (Minimum, Maximum)	13.25 (1.9, 15.9)	2.10 (0.2, 6.9)
Sex, n (%)		
Male	6 (60.0)	11 (61.1)
Female	4 (40.0)	7 (38.9)

JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome.
[a] Age in years was calculated as: (Date of informed consent – Date of birth + 1)/365.25.
Source: Table 14.1.5.

Table 3 Baseline Disease Characteristics (ITT)

Parameter	Myelodysplastic Syndrome (MDS) (N=10)	Juvenile Myelomonocytic Leukemia (JMML) (N=18)
Time from Initial Diagnosis (days) [a]		
n	10	18
Mean	8.4	23.9
StdDev	6.93	17.13
Median	7.5	24.5
Q1, Q3	4.0, 11.0	8.0, 34.0
Min, Max	1, 25	1, 73
MDS Diagnosis - n (%)		
Primary	10 (100)	
Secondary	0	
MDS Classification - n (%)		
Refractory Anemia with Excess Blasts (RAEB)	6 (60.0)	
RAEB in transformation (RAEB-t)	4 (40.0)	
Secondary MDS presenting as CMML without increase in blasts but with chromosomal abnormality	0	
JMML Diagnosis - n (%)		
Somatic Mutation in PTPN11		13 (72.2)
Somatic Mutation in KRAS		1 (5.6)
Somatic Mutation in NRAS with percentage of HbF higher than 5 times the normal value for age		3 (16.7)
Clinical Diagnosis of Neurofibromatosis Type 1 (NF1)		1 (5.6)
At least 6 café-au-lait macules greater than 5 mm in diameter		1 (5.6)
A first degree relative with NF1		0

CHMP comment:

While patient numbers are limited, the studied population seems to be a reasonable representation of the general MDS and JMML paediatric patient population.

Data on medical history at study entry and concomitant active conditions, prior and concomitant therapies and or procedures were collected. The reported concomitant medications were consistent with underlying disease of the subjects enrolled in the study.

Pharmacokinetic results

Mean plasma concentrations of azacitidine on Day 7 for the PK Population of Study AZA-JMML-001 at a 75 mg/m^2 dose are summarized in Figure 2. Both in the paediatric MDS and JMML population, mean azacitidine plasma concentration-time profiles appeared well characterized over the 6-hour post-dose sampling interval. The plasma PK parameters following azacitidine administration are summarized in Table 4.

As expected, azacitidine rapidly reached maximum plasma concentration within 0.083 hours (5 min) post IV administration in both MDS and JMML populations. Visual inspection of mean plasma concentrations of azacitidine time profiles following azacitidine administration suggested that azacitidine plasma exposures appeared to be similar between the MDS and JMML populations. The t½ were 0.4 and 0.3 hours, and the CL were 166.4 and 148.3 L/h for MDS and JMML, respectively (Table 4).

Following IV administration of azacitidine, the Cmax were 1797.5 and 1066.3 ng/mL, and the AUC0-t were 628.9 and 386.9 h·ng/mL, for MDS and JMML subjects, respectively. The Vz were 103.9 and 61.1 L for MDS and JMML subjects, respectively. It appeared that the total plasma exposure of azacitidine was higher in MDS subjects, however, moderate to high between-subject variability was noted for both AUC and Cmax (Table 4).

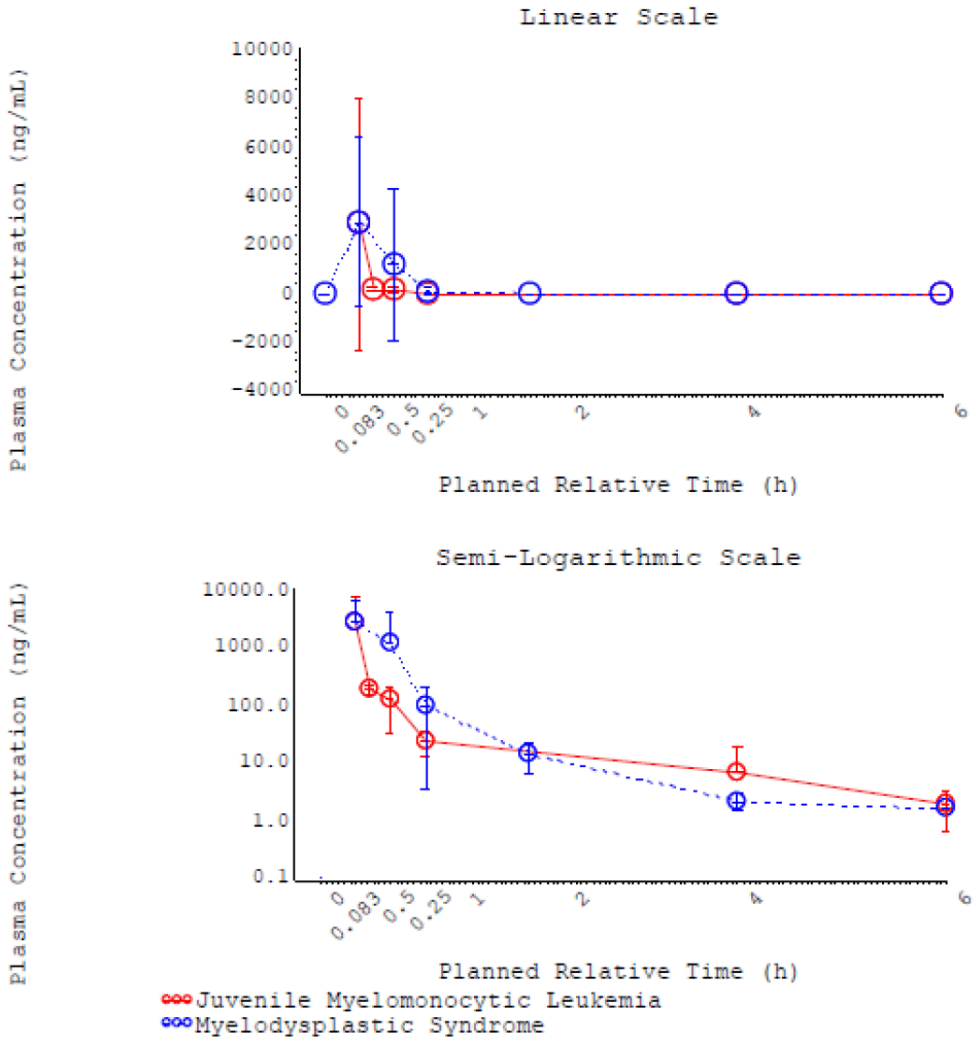


Figure 2 Mean (± SD) azacitidine plasma concentrations – time profiles on day 7 (Pharmacokinetic population Study AZA-JMML-001)

Table 4 Geometric mean (geometric CV %) of azacitidine plasma pharmacokinetic parameters – Day 7 at a dose of 75 mg/m² (Pharmacokinetic population Study AZA-JMML-001)

Azacitidine Parameter	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-t} (h·ng/mL)	AUC_{0-24} (h·ng/mL)	$AUC_{0-\infty}$ (h·ng/mL)	$t_{½}$ (h)	CL (L/h)	V_z (L)
MDS (N = 10)	1797.5 (133.6)	0.083 (0.00-0.50)	629.1 (123.1)	634.8 (122.2)	606.9[b] (131.6)	0.4[b] (22.7)	166.4[b] (135.6)	103.9[b] (122.0)
JMML (N = 18)	1066.3 (215.3)	0.083 (0.03-0.33)	386.9 (149.4)	394.4 (145.9)	240.2[c] (76.5)	0.3[c] (58.4)	148.3[c] (104.2)	61.1[c] (125.8)

AUC_{0-24} = area under the plasma concentration time curve from time zero to 24 hours post dose; 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; JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome; PK = pharmacokinetic; $t_{½}$ = half-life in terminal phase; t_{max} = time to maximum plasma concentration; V_z = volume of distribution.

[a] Median (minimum-maximum)

[b] n = 9

[c] n = 12

CHMP comment:

Azacitidine rapidly reached maximum plasma concentration within 5 minutes post IV administration in both the MDS and JMML population. Visual inspection of mean plasma concentrations of azacitidine time profiles following azacitidine administration suggested that azacitidine plasma exposures are similar between the MDS and JMML populations, with only a trend for higher exposure in MDS patients. It is agreed with the Applicant that due the high variation in azacitidine PK and the low number of subjects, conclusions on potential differences in exposure between MDS and JMML patients should be taken with caution.

Based on interstudy comparison, exposure to azacitidine in paediatric patients 0-17 following IV administration of a 75 mg/m^2 dose appears in the same range as that in adults following IV administration of the same dose. Considering the high absolute bioavailability of 89%, exposure is expected to be also comparable to that obtained in adults after SC administration of a 75 mg/m^2 dose. This comparable exposure is in support of IV use at a 75 mg/m^2 dose in JMML. PK data in paediatric patients has been described in SmPC section 5.2.

Biomarker correlation analysis

Azacitidine incorporates into both DNA and RNA resulting in cellular differentiation, arrest, and/or cytotoxicity and inactivation of DNA methyltransferases, leading to DNA hypomethylation, which was utilized as a key pharmacodynamic (PD) marker of azacitidine activity. Bone marrow (BM) genomic DNA methylation was to be analysed across all time points for both the JMML and MDS disease indications. However due to discontinuation of the MDS arm because of futility, biomarkers were not analysed for this population.

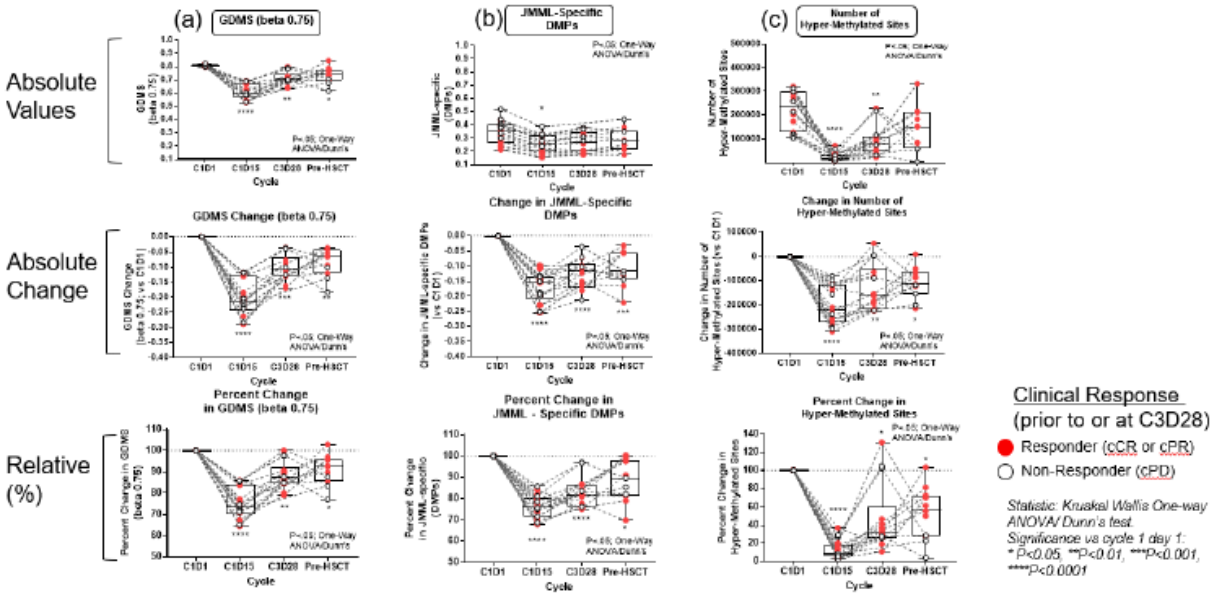
The PD effects of azacitidine on DNA methylation in JMML subjects were investigated by computing: (1) the methylation levels of all CpG probes that were highly methylated at baseline; (2) the number of highly methylated CpG probes across all time points; and (3) the JMML-specific DNA methylation score derived from differentially methylated probes (JMML DMPs), across all time points (Lipka, 2017).

At baseline, JMML subjects exhibited varied BM DNA methylation levels. Azacitidine treatment led to reductions in DNA methylation in all 18 JMML subjects (see Figure 3). Recovery of methylation to near-baseline levels occurred at Cycle 3 Day 28, during the period of drug withdrawal (Cycle 3 Day 28 and pre-HSCT).

PK-PD analysis suggests that there is no apparent correlation between exposure (Cmax and AUC) and PD readouts (Global DNA methylation scores, JMML-specific DMP scores, or the number of hypermethylated sites).

DNA methylation changes appeared to be similar between responder and nonresponder subsets at Cycle 3 Day 28 (versus Cycle 1 Day 1; Kruskal Wallis one-way ANOVA and Dunn's test; $p < 0.05$; not significant). No statistically significant association was observed between the high methylation class compared to the intermediate methylation class on confirmed response at Cycle 3 Day 28; however, a statistically significant association was observed against the low and intermediate JMML methylation classes (Fisher's exact test for association, $p = 0.049$).

No association was observed between the various DNA methylation readouts at baseline with TTR, TTP, or LFS.



ANOVA = analysis of variance; cCR = clinical complete remission; cPD = clinical progressive disease; cPR = partial response; DMP = differentially methylated probe; DNA = deoxyribonucleic acid; GDMS = global DNA methylation scores; HSCT = hematopoietic stem cell transplantation; JMML = juvenile myelomonocytic leukemia
Kruskal Wallis one-way ANOVA/ Dunn's test. Significance versus Cycle 1 Day 1: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.
Sources: Listing 16.2.6.12, Listing 16.2.6.5.2, Table 14.2.11.1, and Figure 14.2.11.1.

Figure 3 Pharmacodynamic Reductions in DNA Methylation with Azacitidine Treatment in JMML Subjects

CHMP comment:

The fact that a reduction in methylation was seen in all treated JMML subjects indicates that azacitidine was pharmacodynamically active in all treated subjects. No relationship between exposure and change in methylation was noted. This might suggest that saturation of the PD effect occurred, assuming that the PD effect is exposure dependent. However the accuracy of this assumption is not known.

In any case it is not expected that increasing the dose would lead to an increase in clinical response.

Efficacy results

Primary Efficacy Endpoint:

For MDS subjects, there were no confirmed response based on central review (confirmed response rate of 0% [95% CI = 0.0, 30.8])(see Table 5). No subjects achieved a CR or PR, but 1 subject (10.0%) achieved a marrow CR (finding not confirmed) and 3 MDS subjects had a missing unconfirmed hematologic response (but were discontinued prior to Cycle 3 Day 28).

Table 5 Central review response rate for subjects with MDS at cycle 3 day 28

Parameter	MDS Subjects (N = 10)
Confirmed Hematologic Response[a], n	
Complete Remission	0
Partial Remission	0
Marrow Complete Remission	0
Confirmed Response Rate[a,b], n (%)	0
95% Confidence Interval[c]	0.0, 30.8
Unconfirmed Hematologic Response[a], n (%)	
Complete Remission	0
Partial Remission	0
Marrow Complete Remission	1 (10.0)
Stable Disease	1 (10.0)
Relapse after Complete Remission or Partial Remission	0
Progression Disease	5 (50.0)
Missing[a]	3 (30.0)
Cytogenetic Response[a], n (%)	
Yes	1 (10.0)
No	6 (60.0)
Missing[a]	3 (30.0)

HSCT = hematopoietic stem cell transplantation; MDS = myelodysplastic syndrome.

[a] Response as assessed by the modified International Working Group Response Criteria for MDS (Cheson, 2006). Subjects with a response observed after HSCT were censored. Responses occurring after start of a new anticancer therapy were censored. Subjects classified as 'Missing' did not have a Cycle 3 Day 28 assessment due to having discontinued from study treatment prior to this point.

[b] Confirmed response was defined as either complete remission, partial remission, or marrow complete remission that was sustained for 4 weeks prior to or after Cycle 3 Day 28.

[c] Clopper Pearson's exact binomial confidence interval.

Sources: Table 14.2.1.1.1 and Listing 16.2.6.5.1.

For JMML subjects, there were a total of 11 subjects with clinical response at Cycle 3 Day 28 (4 subjects [22.2%] with cCR and 7 subjects [38.9%] with cPR) (see Table 6). Of these 11 subjects, 9 (50%) subjects had a confirmed clinical response (3 subjects with cCR and 6 subjects with cPR). The 2 JMML subjects who had a missing unconfirmed haematologic response were discontinued prior to Cycle 3 Day 28.

Table 6 Central review response rate for subjects with JMML at cycle 3 day 28.

Parameter	JMML Subjects (N = 18)
Confirmed Clinical Response[a], n (%)	
Clinical Complete Remission	3 (16.7)
Clinical Partial Remission	6 (33.3)
Confirmed Response Rate[a] [b], n (%)	9 (50.0)
95% Confidence Interval[c]	26.0, 74.0
Unconfirmed Clinical Response[a], n (%)	
Clinical Complete Remission	4 (22.2)
Clinical Partial Remission	7 (38.9)
Clinical Stable Disease	0
Clinical Relapse	0
Clinical Progressive Disease	5 (27.8)
Missing[a]	2 (11.1)
Genetic Response[a], n (%)	
Yes	2 (11.1)
No	14 (77.8)
Missing[a]	2 (11.1)

HSCT = hematopoietic stem cell transplantation; JMML = juvenile myelomonocytic leukemia.

[a] Response as assessed by the International JMML response criteria (Niemeyer, 2015). Subjects with a response observed after HSCT were censored. Responses occurring after start of a new anticancer therapy were censored. Subjects classified as 'Missing' did not have a Cycle 3 Day 28 assessment due to having discontinued from study treatment prior to this point.

[b] Confirmed response was defined as either clinical complete remission or clinical partial remission that was sustained for 4 weeks prior to or after Cycle 3 Day 28.

[c] Clopper Pearson's exact binomial confidence interval.

Sources: Table 14.2.1.1.1 and Listing 16.2.6.5.1.

Similar findings were noted for the PP Population.

As a sensitivity analysis for JMML only, the response assessment at Cycle 3 Day 28 was to be assessed according to the updated response assessment criteria. Based on these updated response criteria all 11 (61.1%) subjects were considered partial responders.

The characteristics of the responder (N = 11) and non-responder (N = 7) JMML subjects at Cycle 3 Day 28 are provided in Table 6 and Table 7. The responder subjects are in the lower ages (from 0.2 to 4.7 years old). All the subjects with low or intermediate methylation (LM and IM) class and 4 subjects with high methylation (HM) class had clinical response. Subjects with unfavourable prognosis, such as subjects with PTPN11 mutation and HM status, responded to azacitidine treatment. Subjects who progressed at Cycle 3 Day 28 had unfavourable prognosis: they are in the higher ages (from 1.8 to 6.9 years old), most of them had PTPN11 mutation, and all had HM status.

No statistically significant association was observed between the HM class compared to the IM class on confirmed response at Cycle 3 Day 28; however, a statistically significant association was observed against the IM+LM classes (Fisher's exact test for association, p = 0.049).

Table 7 Characteristics of the JMML Subjects With a Clinical Response to Azacitidine Treatment at Cycle 3 Day 28

[redacted]	Molecular Genetics	Karyotype	Methylation Class	Number of Treatment Cycles	Confirmed Clinical Response	Clinical Response (sensitivity analysis)	HSCT (yes/no)	Survival to date (yes/no)[c]
	PTPN11	Normal	Low	6	cCR	cPR	Yes	Yes
	PTPN11	Normal	Low	3	cCR	cPR	Yes	Yes
	PTPN11	Normal	High	6	cCR	cPR	Yes[a,b]	Yes
	NRAS	Normal	Intermediate	4	cPR	cPR	Yes	Yes
	PTPN11	-7	Intermediate	6	cPR	cPR	Yes	Yes
	PTPN11	Normal	High	3	cPR	cPR	Yes[b]	Yes
	PTPN11	-7	Intermediate	6	cPR	cPR	Yes	Yes
	NRAS	Normal	High	3	cPR	cPR	Yes	Yes
	KRAS	-7	Intermediate	3	cPR	cPR	Yes	Yes
	PTPN11	+21c	Intermediate	3	No	cPR	Yes	Yes
	PTPN11	Normal	High	3	No	cPR	Yes	Yes

cCR = clinical complete remission; cPR = clinical partial remission; HSCT = hematopoietic stem cell transplantation.
[a] This subject relapsed after HSCT
[b] This subject received 2 transplants
[c] Data cutoff date: 13 Mar 2019
Sources: Listing 16.2.1.2, Listing 16.2.4.1.2, Listing 16.2.4.1.3, Listing 16.2.5, Listing 16.2.6.1.2, Listing 16.2.6.5.1, Listing 16.2.6.5.2, Listing 16.2.6.7, and Listing 16.2.6.12.

Table 8 Characteristics of the JMML Subjects who did not Respond to Azacitidine Treatment at Cycle 3 Day 28

[redacted]	Molecular Genetics	Karyotype	Methylation Class	Number of Treatment Cycles	Clinical Response	Clinical Response (sensitivity analysis)	HSCT (yes/no)	Survival to date (yes/no)[a]
	PTPN11	del(9)	High	3	cPD	cPD	Yes[b]	No[c]
	PTPN11	Normal	High	3	cPD	cPD	Yes	Yes
	NRAS	Normal	High	3	cPD	cPD	Yes	Yes
	PTPN11	Normal	High	4	cPD	cPD	Yes[d]	Yes
	PTPN11	Normal	High	3	cPD	cPD	Yes	Yes
	PTPN11	Normal	High	1	Missing	Missing	No	No[e]
	NF-1	Not assessed	High	2	Missing	Missing	Yes	Yes

cPD = clinical progressive disease; HSCT = hematopoietic stem cell transplantation.
[a] Data cutoff date: 13 Mar 2019
[b] This subject received 2 transplants
[c] Subject [redacted]: death due to HSCT toxicity
[d] This subject relapsed after HSCT
[e] Subject [redacted]1: death due to clinical PD
Sources: Listing 16.2.1.2, Listing 16.2.4.1.2, Listing 16.2.4.1.3, Listing 16.2.5, Listing 16.2.6.5.1, Listing 16.2.6.5.2, Listing 16.2.6.7, and Listing 16.2.6.12.

CHMP comment:

Methylation status is a prognostic factor for JMML, with high methylation indicting a worst prognosis. It is noted that while azacitidine is a demethylating agent, all non-responding subjects had a high methylation status.

Secondary Efficacy Endpoints

For the secondary efficacy endpoints, the median follow-up time for the MDS subjects was 25.7 months (range: 24.9 to 29.5 months), while the median follow-up time for the JMML subjects was 22.7 months (range: 14.0 to 30.5 months)

MDS group (n=10 subjects)

One (1) subject (10.0%) experienced a response with a median time to response (TTR) of 2.76 months, the duration of response, with censoring for HSCT, could not be estimated. The cytogenetic response rate was 10.0% (1 subject) (see Table 4).

The median time to progression (TTP) with censoring for HSCT was 0.97 months (95% CI = 0.95, 2.04) with 9 subjects (90.0%) having disease progression or death due to progression with censoring for HSCT. The median LFS time could not be estimated. The leukemia free survival (LFS) rate at 6 months post HSCT, 12 months post HSCT, and at time of analysis was 100.0%, 100.0%, and 80.0%, respectively. One (1) subject died during FU.

All 10 MDS subjects received HSCTs, the median time to HSCT was 3.76 months (95% CI = 2.79, 4.73). All 10 subjects (100%) had at least 1 transfusion (both RBC and platelet) during the study with a median number of 19.0 transfusions (range: 7 to 101). Prior to dosing, 6 subjects (60.0%) had at least 1 infusion with a median number of 6.0 transfusions (range: 4 to 17) and after dosing prior to HSCT, 7 subjects (70.0%) had at least 1 infusion with a median number of 7.0 transfusions (range: 1 to 92).

CHMP comment

It is noted that the one subject with a (non-confirmed) response had also a cytogenetic response. While most patients had progressive disease at the time of HSCT, LFS after HSCT was 100% at 12 months following HSCT signifying the curative effect of transplantation.

JMML group (n=18 subjects)

Twelve (12) subjects (66.7%) experienced a response during the treatment period prior to transplant with a median TTR duration of 1.20 months (95% CI = 0.95, 1.87). A median duration of response could not be estimated. The genetic and molecular responses were noted in 2 subjects (11.1%), both clinical responders)(see Table 6).

The median TTP could not be estimated, with 8 subjects (44.4%) having disease progression with censoring for HSCT. The median LFS time (ITT Population) could not be estimated. The LFS rate at 6 months post HSCT, 12 months post HSCT, and at time of analysis was 87.8%, 81.6%, and 81.6%, respectively. Two subjects died during FU. The OS rate at 6 months, 12 months, and at time of analysis was 94.4%, 88.9%, and 88.9%, respectively.

17 JMML subjects received HSCTs, the median time to HSCT was 4.63 months (95% CI = 3.91, 6.77). All 18 subjects (100%) had at least 1 transfusion (17 subjects had both RBC and platelet) during the study with a median number of 14.5 transfusions (range: 1 to 162). Prior to dosing, 15 subjects (83.3%) had at least 1 infusion with a median number of 3.0 transfusions (range: 1 to 18) and after

dosing prior to HSCT, 4 subjects (22.2%) had at least 1 infusion with a median number of 20.5 transfusions (range: 3 to 37).

CHMP comments:

Most time dependent endpoints are difficult to interpret because of the HSCT following treatment. It is noted that time to response is generally rapid and occurs within the first two cycles (so if a patient does not respond after 2 cycles it is likely that the patient will not respond at all).

It is noted that while the responses to azacitidine were mostly partial responses, the vast majority of patients were leukaemia free following HSCT, demonstrating the anti-JMML effect of HSCT.

The 2 deaths are due to disease progression and sepsis (see safety section).

In the study report for the secondary endpoint of time to response it is stated that 12 subjects experienced a response during treatment, while for the primary endpoints 11 subjects were stated to have a response of which 9 were confirmed. This discrepancy in patient numbers has not been explained. Possibly 1 additional patient experienced a response but not on the time point for the primary endpoint (i.e. Cycle 3 Day 28). In case this study would be used for an extension of indication, clarification on this discrepancy should be provided.

While 18 JMML subjects were treated with azacitidine, 17 received HSCT. In the study report it was not clearly stated why one JMML subject did not receive a HSCT. But again, clarification should be provided in case this study would be used as basis for an extension of the indication.

Efficacy conclusions

No response was confirmed in any MDS subject and only 1 subject (10.0%) achieved an unconfirmed marrow CR. These data indicated lack of efficacy in MDS subjects and the MDS arm was closed after Stage 1. The secondary efficacy endpoint of cytogenetic response to azacitidine was achieved by 1 MDS subject (10.0%) with time to response 2.76 months. Median TTP (with censoring for HSCT) was 0.97 months for 9 MDS subjects (90.0%). All MDS subjects underwent HSCT, one subject died during the study, all other subjects were censored at the time of the analysis.

There was a total of 11 JMML subjects with clinical response at Cycle 3 Day 28 (4 subjects [22.2%] with cCR and 7 subjects [38.9%] with cPR). Of these 11 subjects, 9 (50%) subjects had a confirmed clinical response (3 cCR and 6 cPR). The median TTR was 1.20 months for 12 JMML subjects (66.7%). According to the Applicant, these results show that the azacitidine treatment prior to HSCT was effective in JMML and provided clinical benefit to subjects in this study. The secondary efficacy endpoint of genetic and molecular response to azacitidine was achieved by 2 JMML subjects (11.1%).

Median time to progression data could not be estimated for JMML subjects when censored for HSCT. The proportion of subjects undergoing HSCT was 94.4% (n=17). 2 subjects (11.1%) in the JMML arm died during the study, and all other subjects were censored at the time of the analysis.

CHMP comments:

Data on the effect of azacitidine in children with MDS are limited. Responses to treatment have been reported, but at a rather low frequency and not all authors have observed responses following azacitidine treatment (Waespe et al Haematologica 2016, Cseh et al BJH 2016, van Eijkelenburg EHA 2019). In the current study only 1 non-confirmed clinical response was noted, albeit accompanied by a cytogenetic response. This indicates only limited activity of azacitidine in paediatric MDS. This seems particularly limited in relation to the effect of the subsequent HSCT on disease, where all subjects (initially) became disease free. Overall, the added value of treatment of azacitidine as a bridge to HSCT in children with MDS seems limited. As azacitidine was shown to slow progression to leukaemia in

adults with MDS, the limited activity in paediatric MDS is relevant information to the prescriber and this information is provided in the SmPC.

Data on the effect of azacitidine in JMML in the public domain seems even more limited than for MDS. Case reports suggest activity of azacitidine against JMML. Indeed, the current study confirms that azacitidine is able to reduce disease burden in approximately 50% of newly diagnosed JMML patients. However, and as discussed above the clinical relevance of this finding is not clear. HSCT seems very efficacious in eliminating the disease (~90% was disease free following HSCT), and data to support the assumption that lower tumour burden prior to HSCT improves long term outcomes are limited to cross study comparison involving historical controls which is insufficient in this respect (see discussion below). Thus the uncertainty in the translation of anti-disease activity into clinical benefit impedes the possibility of balancing the risks against benefits of treatment as the benefits cannot be estimated. Furthermore, as JMML is a childhood disease extrapolation from adult data is not possible.

As the observed activity of azacitidine in (paediatric) patients with JMML is of interest to the physicians, this information is provided in the SmPC.

Comparison to historical controls

In order to understand the survival benefit of azacitidine in the context of conventional therapies available for paediatric subjects with JMML, the AZA-JMML-001 efficacy data were to be compared retrospectively to data from subsets of patients from the EWOG-MDS registry that met the key eligibility criteria of the AZA-JMML-001 study.

The objective of this analysis was to compare the efficacy results from Study AZA-JMML-001 in subjects treated before HSCT with IP at 75 mg/m², QD on Days 1 to 7 of a 28-day cycle to JMML patients in the historical control arm by:

1. Relativizing platelet transfusion independency and sustained platelet counts obtained in the AZA-JMML-001 study to that observed in a cohort of patients untreated with azacitidine. For the purpose of this comparison, the primary endpoint was defined as proportion of subjects achieving self-sustained platelet count self-sustained pre-HSCT platelet count above a specified threshold (either 50, 100, or 150×10^9/L), which was a surrogate marker for response.

2. Relativizing OS and post-HSCT survival observed in the AZA-JMML-001 study to those observed in a cohort of patients untreated with azacitidine.

In summary, the methodology consisted of:

- Mapping of the 2 groups of patients according to the 2 major prognostic factors: age at diagnosis of JMML and platelets level at diagnosis.
- Identification of 2 matched subsets of patients with similar profiles according to the 2 major prognostic factors.
- The primary endpoint comparison was performed using Fisher's exact test.
- Kaplan-Meier's curves for OS and comparison using unstratified and stratified Cox's model, both for the full patient set and for the matched subset.

Patient selection and clinical characteristics of the historical control cohort are described in a separate study report (EWOG-MDS Study Report, March 2019).

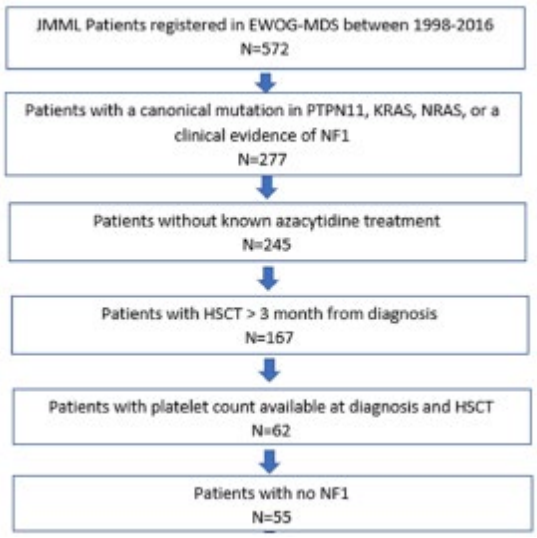


Figure 4 Selection Criteria for JMML Patients From the EWOG-MDS Registry

A total of 55 patients were selected for the comparison analysis according to the following criteria: canonical mutation in PTPN11, KRAS, NRAS, no azacitidine therapy, HSCT > 3 months from diagnosis, platelet count available at diagnosis and HSCT, and no NF-1 (see Figure 2). Thirty-two patients of the historical control cohort had received 6-mercaptopurine or other low-dose chemotherapy, 4 patients had been given AML therapy and 10 patients had not received any therapy prior to HSCT. Data for therapy were not available for 9 patients.

Table 9 Clinical Characteristics of the Historical Control Cohort With Respect to JMML subtype

	All (N = 55)	PTPN11 (N = 38)	KRAS (N = 13)	NRAS (N = 4)
Gender (Male/Female) n (%)	39/16 (71%/29%)	24/14 (63%/37%)	11/2 (85%/15%)	4/0 (100%/0%)
Age at Diagnosis (years) Median (Range)	1.6 (0.1 – 11.2)	2.3 (0.2 – 11.2)	0.7 (0.1 – 2.2)	1.5 (1.0 – 3.2)
Age at HSCT (years) Median (Range)	2.0 (0.5 – 11.5)	2.8 (0.5 – 11.5)	1.2 (0.5 – 3.7)	2.0 (1.3 – 3.6)
Platelets at Diagnosis (10^9/L) Median (Range)	56 (5 – 205)	56 (5 – 205)	59 (27 – 113)	45 (31 – 56)
Platelet Count HSCT (10^9/L) Median (Range)	43 (5 – 356)	40 (5 – 356)	52 (19 – 123)	28 (9 – 35)
Therapy, n (%)				
6-MP With or Without Low Dose Chemotherapy	32 (70%)	21 (70%)	8 (67%)	3 (75%)
AML Induction	4 (9%)	4 (13%)	0	0
None	10 (22%)	5 (17%)	4 (33%)	1 (25%)
No Data	9	8	1	0

6-MP = mercaptopurine; AML = acute myeloid leukemia; HSCT = hematopoietic stem cell transplantation; JMML = juvenile myelomonocytic leukemia.
Source: EWOG-MDS Study Report, March 2019.

After a median follow-up after diagnosis of 5.6 years (range: 0.6 to 17.9), 39 of the 55 patients are alive, resulting in a probability of 5-year OS of 0.68 (range: 0.55 to 0.81). The outcome from HSCT

resulted in a 5-year LFS of 0.57 (range: 0.43 to 0.71), while the cumulative incidence of non-relapse mortality and relapse were 0.11 (range, 0.05 to 0.23) and 0.32 (range, 0.22 to 0.48), respectively.

The control cohort was further refined to exclude the subjects with age greater than 7 years and platelet count greater than 100 × 10^9/L from the analysis in order to limit the comparison to the same range of baseline characteristics of these 2 parameters in the AZA-JMML-001 cohort. This resulted in 44 patients being selected from the historical control cohort to be used for the analysis. Eighteen subjects were treated with azacitidine in the AZA-JMML-001 study. Two subjects were excluded from the analysis of the surrogate endpoint for the comparison: 1 subject who expressed NF-1 mutation due to high platelet count at diagnosis based on the selection criteria and another subject due to death prior HSCT. This resulted in 16 subjects being selected from the AZA-JMML-001 study.

A higher percentage of subjects required transfusion at diagnosis in the AZA-JMML-001 cohort compared to the historical control cohort (68.8% versus 11.4%, p < 0.0001). After treatment (pre-HSCT), the percentage of subjects who required transfusion was lower in the AZA-JMML-001 cohort compared to the historical control cohort (43.8% of subjects versus 63.6%, p = 0.2375).

Table 10 Self-sustained Platelet Count at Hematopoietic Stem Cell Transplantation in AZA-JMML-001 Cohort Versus Historical Control

Description	AZA-JMML-001 (N = 16)	Historical Cohort (N = 44)	p-value[a]
Patients requiring transfusion at diagnosis, n (%)	11 (68.8)	5 (11.4)	< 0.0001
Patients requiring transfusion at HSCT, n (%)	7 (43.8)	28 (63.6)	0.2375
Self-sustained platelet count at HSCT, n (%)			
≥ 50 × 10^9/L	9 (56.3)	9 (20.5)	0.0116
≥ 100 × 10^9/L	7 (43.8)	4 (9.1)	0.0051
≥ 150 × 10^9/L	5 (31.3)	1 (2.3)	0.0040

HSCT = hematopoietic stem cell transplantation.
[a] Fisher's exact test.
Source: Table 14.2.14.2.

Table 11 Overall Survival Rate on the Matched Subsets of AZA-JMML-001 and Historical Control Cohorts

Overall Survival Rate	AZA-JMML-001 (N = 16)	Historical Cohort (N = 44)
At 6 months (95% CI), %	100.0	97.7 (84.9, 99.7)
At 1 year (95% CI), %	93.8 (63.2, 99.1)	74.4 (58.5, 84.9)
At 2 years (95% CI), %	93.8 (63.2, 99.1)	69.5 (53.3, 81.0)

CI = confidence interval.
Source: Table 14.2.14.3.

Subjects in the AZA-JMML-001 study treated with azacitidine showed a clinical benefit with platelet responses compared to the matched historical cohort, with a lower percentage of subjects requiring transfusions at HSCT in the AZA-JMML-001 experimental arm (43.8%) versus the historical cohort (63.6%) and significantly higher number of subjects in AZA-MML-001 cohort with sustained platelet counts.

Furthermore, subjects in the AZA-JMML-001 study treated with azacitidine appear to show more favourable survival than subjects from the historical control cohort, although confounding factors such as improvements in HSCT methods over time need to be taken into consideration.

CHMP comment:

As noted above, the benefit of reducing the tumour burden in JMML prior to HSCT for long term outcomes cannot be determined based on study AZA-JMML-001 as an internal control is lacking and extrapolation from adults is not possible. To contextualise the results, the MAH has provided a comparison with an external historical control group based on the EWOG-MDS registry. This is much appreciated. The results of this comparison indicate that azacitidine may reduce transfusion requirements prior to HSCT. However whether this results in an improved success rate of HSCT is not clear. The comparison also suggest that azacitidine treatment prior to HSCT may result in a higher OS rate. However, it should be noted that this comparison is accompanied by significant uncertainties. It is based on a small number of patients with a heterogeneous disease who are matched for two prognostic factors only (age and platelet counts). In this comparison the death of one subject already changes the OS rate significantly, in particular in the JMML group. Furthermore, there are additional differences between the two cohorts, e.g. in the median duration of follow up (22 months vs > 5 years) and the time of treatment which have not been accounted for in the comparison. Importantly, a significant number of subjects in the historical control group died of HSCT-related mortality (TRM), while no subject died due to TRM in the JMML cohort. This difference in TRM is most likely due to improved HSCT practices (recent studies indicate significant improvement of TRM in time) and not due to azacitidine treatment.

In conclusion, given these uncertainties, it is not possible to conclude on whether azacitidine prior to HSCT improves survival outcome after HSCT.

Of note, in this comparison it is stated that 7 JMML subjects who received azacitidine required transfusion prior to HSCT, however at the description of the study results it is stated that 4 required transfusion at the time of HSCT. This discrepancy need to be clarified in case this study would be used as basis for an extension of the indication.

Safety results

Exposure to azacitidine is summarized in Table 8.

Table 12 Treatment Exposure (Primary and Safety Population)

Exposure	MDS Subjects N = 10	JMML Subjects N = 18	Overall Subjects N = 28
Treatment Duration (weeks)[a]			
Mean (Standard Deviation)	11.19 (2.336)	15.74 (7.177)	14.11 (6.260)
Median (Minimum, Maximum)	12.00 (5.0, 12.7)	12.29 (4.0, 30.6)	12.00 (4.0, 30.6)
Total Number of Treatment Cycles Completed			
Mean (Standard Deviation)	2.8 (0.42)	3.8 (1.58)	3.5 (1.37)
Median (Minimum, Maximum)	3.0 (2, 3)	3.0 (1, 6)	3.0 (1, 6)
Total Number of Subjects Completing Each Treatment Cycle, n (%)			
Cycle 1	10 (100.0)	18 (100.0)	28 (100.0)
Cycle 2	10 (100.0)	17 (94.4)	27 (96.4)
Cycle 3	8 (80.0)	16 (88.9)	24 (85.7)
Cycle 4	0	7 (38.9)	7 (25.0)
Cycle 5	0	6 (33.3)	6 (21.4)
Cycle 6	0	5 (27.8)	5 (17.9)
Total Number of Doses Received			
Mean (Standard Deviation)	19.5 (3.17)	26.6 (10.91)	24.0 (9.50)
Median (Minimum, Maximum)	21.0 (13, 21)	21.0 (7, 42)	21.0 (7, 42)
Average Weekly Dose (mg/m^2/week)[b]			
Mean (Standard Deviation)	516.0 (15.70)	473.7 (76.03)	488.8 (64.40)
Median (Minimum, Maximum)	522.3 (488, 536)	509.2 (304, 539)	518.0 (304, 539)

JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome.

[a] For subjects who discontinued prior to the clinical cutoff date, treatment duration was defined as ([Last day of investigational product administration] – [Cycle 1 Day 1 of Treatment] + 1)/7. For subjects who were still on treatment at the time of study closure or clinical cutoff, treatment duration was defined as ([Day 1 of treatment of last cycle + 27] – [Cycle 1 Day 1 of Treatment] + 1)/7.

[b] Defined as (total cumulative dose in mg/m^2)/(# of days dosed (received non-zero dose)/7 where number of days dosed is the number of days that a non-zero dose was received.

Each cycle calculated as the time period from Day 1 of each cycle to one day prior to Day 1 of subsequent cycle; for the last treatment period cycle, 27 days after first dose of the last cycle will be used as the treatment end date.

Sources: Table 14.3.1.1.1 and Table 14.3.1.1.2.1.

For MDS subjects (N = 10), 8 subjects completed the 3 cycles as per protocol, 1 subject completed 2 cycles and 1 subject did not complete Cycle 2. In addition to these two subject one additional subject subjects discontinued study treatment (after cycle 3). Reasons for discontinuations were physician decision (n=2) and AE (n=1).

For JMML subjects (N = 18), 16 subjects completed treatment as per protocol (16 subjects completed 3 cycles, and 5 subjects completed 6 cycles), 1 subject completed 1 cycle and 1 subject completed 2 cycles. In addition to these 2 subjects one additional subject discontinued study treatment during the 5th cycle. Reasons for discontinuations were disease progression (n=2) and AE (n=1).

An overview of TEAEs reported is provided in Table 13.

Table 13 Overview of Treatment-emergent Adverse Events

Subjects With at Least 1	MDS Subjects (N = 10) n (%)	JMML Subjects (N = 18) n (%)	Overall Subjects (N = 28) n (%)
TEAE	10 (100)	18 (100)	28 (100)
Grade 3 and 4 TEAE	7 (70.0)	10 (55.6)	17 (60.7)
TEAE Related to AZA	7 (70.0)	10 (55.6)	17 (60.7)
Grade 3 and 4 TEAE Related to AZA	3 (30.0)	6 (33.3)	9 (32.1)
Serious TEAE	4 (40.0)	12 (66.7)	16 (57.1)
Serious TEAE Related to AZA	2 (20.0)	3 (16.7)	5 (17.9)
TEAE Leading to Dose Reduction of AZA	0	0	0
Serious TEAE Leading to Dose Reduction of AZA	0	0	0
TEAE Leading to Dose Interruption of AZA	0	0	0
Serious TEAE Leading to Dose Interruption of AZA	0	0	0
TEAE Leading to Discontinuation of AZA	1 (10.0)	2 (11.1)[a]	3 (10.7)
Serious TEAE Leading to Discontinuation of AZA	1 (10.0)	2 (11.1)[a]	3 (10.7)
TEAE Leading to Death	0	0	0

AZA = azacitidine; IP = investigational product; JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome; TEAE = treatment-emergent adverse event.

[a] One subject discontinued due to a TEAE of disease progression, and one subject discontinued due to a TEAE of abdominal pain and acute respiratory distress.

Dose interruption included dose delay, by definition.

Subjects with a Grade 3, Grade 4, or both were summarized on the applicable categories in the table.

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

Source: Table 14.3.1.2.

Overall, all 28 subjects experienced at least 1 TEAE during the study. Serious TEAEs, Grade 3 and 4 TEAEs, and TEAEs related to the IP were reported in 16 subjects (57.1%), 17 subjects (60.7%), and 17 subjects (60.7%), respectively. Three subjects (10.7%) experienced a TEAE leading to drug discontinuation (pyrexia in MDS subject, and disease progression and abdominal pain in 1 JMML subject each with only the pyrexia was suspected to be related to study drug). No TEAEs leading to death, dose reduction, or drug interruption were reported.

A summary of the most frequently reported TEAEs by SOC and PT (in at least 10% of subjects in the Overall group) is provided in Table 14.

Table 14 Treatment-emergent Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term[a]	MDS Subjects (N = 10) n (%)	JMML Subjects (N = 18) n (%)	Overall Subjects (N = 28) n (%)
Subjects With at Least 1 TEAE	10 (100)	18 (100)	28 (100)
Gastrointestinal Disorders	8 (80.0)	12 (66.7)	20 (71.4)
Constipation	4 (40.0)	4 (22.2)	8 (28.6)
Vomiting	3 (30.0)	5 (27.8)	8 (28.6)
Nausea	3 (30.0)	2 (11.1)	5 (17.9)
Diarrhea	0	4 (22.2)	4 (14.3)
Abdominal Pain	0	3 (16.7)	3 (10.7)
General Disorders and Administration Site Conditions	7 (70.0)	11 (61.1)	18 (64.3)
Pyrexia	4 (40.0)	11 (61.1)	15 (53.6)
Blood and Lymphatic System Disorders	7 (70.0)	10 (55.6)	17 (60.7)
Anemia	6 (60.0)	7 (38.9)	13 (46.4)
Thrombocytopenia	4 (40.0)	5 (27.8)	9 (32.1)
Febrile Neutropenia	4 (40.0)	2 (11.1)	6 (21.4)
Neutropenia	1 (10.0)	3 (16.7)	4 (14.3)
Infections and Infestations	4 (40.0)	11 (61.1)	15 (53.6)
Upper Respiratory Tract Infection	1 (10.0)	3 (16.7)	4 (14.3)
Rhinitis	1 (10.0)	2 (11.1)	3 (10.7)
Skin and Subcutaneous Tissue Disorders	4 (40.0)	11 (61.1)	15 (53.6)
Pruritis Generalized	1 (10.0)	3 (16.7)	4 (14.3)
Dermatitis Allergic	1 (10.0)	2 (11.1)	3 (10.7)
Petechiae	1 (10.0)	2 (11.1)	3 (10.7)
Pruritus	0	3 (16.7)	3 (10.7)
Respiratory, Thoracic, and Mediastinal Disorders	3 (30.0)	8 (44.4)	11 (39.3)
Cough	1 (10.0)	4 (22.2)	5 (17.9)
Epistaxis	1 (10.0)	3 (16.7)	4 (14.3)

System Organ Class Preferred Term[a]	MDS Subjects (N = 10) n (%)	JMML Subjects (N = 18) n (%)	Overall Subjects (N = 28) n (%)
Metabolism and Nutrition Disorders	2 (20.0)	5 (27.8)	7 (25.0)
Hyperuricemia	0	3 (16.7)	3 (10.7)

IP = investigational product; JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome; TEAE = treatment-emergent adverse event.

[a] Coded using Medical Dictionary for Regulatory Activities Version 21.0.

Treatment-emergent adverse events included adverse events that started or worsened between the date of first IP dose and 28 days after the date of last IP dose. A subject was counted only once for multiple events within preferred term/system organ class. The TEAEs were sorted by descending frequency for the system organ class and preferred term within system organ class.

Source: Table 14.3.1.3.

The highest proportion of subjects reporting TEAEs presented with Gastrointestinal Disorders (20 subjects [71.4%]), General Disorders and Administration Site Conditions (18 subjects [63.4%]), Blood and Lymphatic System Disorders (17 subjects [60.7%]), Infections and Infestations (15 subjects [53.6%]), Skin and Subcutaneous Tissue Disorders (15 subjects [53.6%]), and Respiratory, Thoracic, and Mediastinal Disorders (11 subjects [39.3%]). The most frequently reported TEAEs (in ≥ 40% of subjects) were pyrexia (15 subjects [53.6%]) and anaemia (13 subjects [46.4%]).

The majority of the Grade 3 and 4 TEAEs were reported in only 1 subject. Grade 3 and 4 TEAEs reported in > 1 subject were anaemia (11 subjects [39.3%]), thrombocytopenia (7 subjects [25.0%]), febrile neutropenia (4 subjects [14.3%]), neutropenia (3 subjects [10.7%]), and abdominal pain and pyrexia (2 subjects [7.1%] each).

At least 1 treatment-related TEAE was reported in 17 (60.7%) subjects. Treatment-related TEAEs reported in > 1 subject were neutropenia and vomiting (3 subjects [10.7%] each) and anaemia, constipation, febrile neutropenia, nausea, pyrexia, and thrombocytopenia (2 subjects [7.1%] each). Grade 3 and 4 treatment-related TEAEs were reported in 9 subjects (32.1%) with the majority of the events reported in only 1 subject overall. Grade 3 and 4 treatment-related TEAEs reported in > 1 subject were neutropenia (3 subjects [10.7%]) and anaemia and febrile neutropenia (2 subjects [7.1%] each).

Overall, 16 (57.1%) subjects experienced at least 1 serious TEAE. The majority of serious TEAEs were reported in 1 subject each. Serious TEAEs reported in > 1 subject were febrile neutropenia and pyrexia (4 subjects [14.3%] each), upper respiratory tract infection (3 subjects [10.7%]), and viral upper respiratory tract infection (2 subjects [7.1%]).

No subject died during the treatment period. Three subjects died after 28 days following the end of treatment. Two subjects (1 MDS and 1 JMML) died due to "death from malignant disease under study, or complication due to malignant disease under study," and 1 JMML subject died due to "death from other cause" (sepsis).

The most common TEAEs of special interest reported were myelosuppression 16 subjects (57.1%) and infections 15 subjects (53.6%), which were expected based on the known pharmacology of azacitidine. The TEAEs of special interest of cardiac disorders were reported in 2 subjects, which were both considered not related by the investigator.

Haematological TEAE of specific interest (neutropenia, 9 subjects (32.1%), thrombocytopenia 9 subjects (32.1%), anemia, 13 subjects (46.4%)) and shifts in haematology laboratory parameters were observed consistent with known pharmacology of azacitidine. These generally worsened from baseline but did not lead to study discontinuation.

No second primary malignancies were reported in the study.

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

CHMP comments:

The overall safety profile is consistent with what is already known from azacitidine. There were no new/unexpected observations. 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.

All subjects experienced TEAE with gastrointestinal events (including constipation and vomiting), hematologic events (including anaemia, thrombocytopenia, and febrile neutropenia) and pyrexia occurring in the majority of subjects. These are also the events which were most commonly considered

related to treatment. Three subjects experienced a TEAE leading to drug discontinuation (pyrexia in MDS subject, and disease progression and abdominal pain in 1 JMML). No subject died due to AE.

Overall, as in adults, treatment-related toxicity is substantial but manageable.

2.3.3. Discussion on clinical aspects

The MAH has submitted the results of a paediatric study (AZA-JMML-001) in which the effect of azacitidine was studied in paediatric patients newly diagnosed with advanced MDS or JMML. Patients were to receive 75 mg/m^2 azacitidine (IV or SC) QD on Days 1 to 7 of a 28-day cycle for a minimum of 3 cycles and a maximum of 6 cycles before proceeding to HSCT. This is the same starting dose as recommended for the approved (adult) indication.

All patients were expected to proceed to HSCT following azacitidine treatment, irrespective of the treatment effect of azacitidine. Which is supported as HSCT is the only curative treatment option for patients with AML and JMML. However, this significantly hampers the interpretability of the clinical relevance of a treatment effect. While an anti-tumour effect may be noted in terms of reduction in disease burden, the added value thereof on clinically relevant outcome measures such as OS or LFS cannot be estimated as this is confounded by HSCT, and while it is intuitively appealing to assume that a reduced tumour burden will increase the curative success of HSCT, this has currently not been shown for (paediatric) patients wilt AML or JMML.

PK analyses indicate that azacitidine rapidly reached maximum plasma concentration within 5 minutes post IV administration in both the MDS and JMML population and that azacitidine plasma exposures are similar between the MDS and JMML populations, with only a trend for higher exposure in MDS patients. However due the high variation in azacitidine PK and the low number of subjects, conclusions on potential differences in exposure between MDS and JMML patients should be taken with caution. An assessment whether drug exposures from IV administration in JMML paediatrics are comparable with that from SC/IV administration in adults, supporting IV use in JMML, was lacking and should be provided. Further only PK data following IV administration were shown while S.C. was allowed under specific conditions. Information should be provided on the number of situations in Study AZA-JMML-001 where azacitidine was administered via the SC route, and if available PK data from the S.C. administration should be provided as well. PK data in paediatric patients should be described in SmPC section 5.2.

For the 10 MDS subjects, no confirmed responses were noted, but 1 subject achieved a (non-confirmed) marrow CR. For the 18 treated JMML patients, there were 9 confirmed responses (3 subjects with CR and 6 subjects with PR based on definition described by Niemeyer, 2015), and 2 additional patients had non-confirmed responses (but were but were discontinued prior to response confirmation on Cycle 3 Day 28 for confirmation).

It is noted that time to response is generally rapid and occurs within the first two cycles. Most of the other time dependent endpoints (DoR, OS, LFS) are difficult to interpret because all but 1 patient proceeded to HSCT and/or a control arm is lacking. Notably, while following azacitidine mostly partial responses were noted, the vast majority patients (both MDS and JMML) were leukaemia free following HSCT demonstrating the anti-leukemic effect of HSCT.

While azacitidine was shown to slow disease progression in adults with MDS, this study indicates limited activity of azacitidine against MDS in paediatric patients. While in literature responses have been reported, this was generally at a low frequency, which seems particularly limited in relation to the effect of the subsequent HSCT on disease, where all subjects (initially) became disease free. Overall, the added value of treatment of azacitidine as a bridge to HSCT in children with MDS seems limited,

this is considered relevant information to the prescriber, therefore this information is provided in the SmPC.

The current study shows that azacitidine is able to reduce disease burden in approximately 50% of newly diagnosed advanced JMML patients. However, the clinical relevance of such a response is difficult to estimate as the added value of a reduction in disease burden prior to HSCT for the outcome of HSCT in terms of OS and LFS, while intuitively appealing, is not known. Extrapolation from adults is not possible (JMML is a childhood disease), and an internal control was not included in the study. The matched pair analyses with a historical control group (matched for age and platelet count only) is accompanied by significant uncertainties which prohibit a conclusion on the effect of azacitidine prior to HSCT on survival outcome after HSCT. The observed activity of azacitidine in (paediatric) patients with JMML is of interest to the physicians, this information is provided in the SmPC.

The observed safety profile is consistent with what is already known from azacitidine. There were no new/unexpected observations. 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. Overall, as in adults, treatment-related toxicity in the paediatric population is substantial but manageable.

Finally, as the patient population in the current study with azacitidine differs from the approved patient population, the here reported efficacy results are not relevant for the approved indications. Moreover, as no new safety signals have been identified, also the safety profile is not changed. Therefore, it is considered that the results of this study do not impact the benefit-risk of azacitidine in the already approved (adult) indications.

3. Request for Supplementary Information requested

Based on the data submitted, the MAH should address the following questions:

1. Only PK data following IV administration were shown in the Study report. Information should be provided on the number of situations in Study AZA-JMML-001 where azacitidine was administered via the SC route. If possible, PK data should be reported separately following IV and SC administration in an updated CSR.

2. A discussion on the azacitidine PK in MDS and JMML patients was lacking in the Clinical Overview and should be provided. Furthermore PK data from the IV route from AZA-JMML-001 in paediatrics should be pooled together with PK data (IV and SC) from adults for an analysis, assessing if the drug exposures from IV administration in JMML paediatrics are comparable with that from SC/IV administration in adults, supporting IV use in JMML. 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 describing the results of this study in a concise and informative manner.

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

MAH responses to Request for supplementary information

1. Only PK data following IV administration were shown in the Study report. Information should be provided on the number of situations in Study AZA-JMML-001 where azacitidine was administered via the SC route. If possible, PK data should be reported separately following IV and SC administration in an updated CSR.

MAH Response to CHMP Question 1

Celgene confirms that all subjects in Study AZA-JMML-001 received azacitidine via the intravenous (IV) administration route. No patient in the study received azacitidine via the subcutaneous (SC) administration route (see clinical study report [CSR] section 12.1).

Assessment of Applicant's response

The Applicant confirmed that all patients received azacitidine via the IV route.

Issue resolved

2. A discussion on the azacitidine PK in MDS and JMML patients was lacking in the Clinical Overview and should be provided. Furthermore PK data from the IV route from AZA-JMML-001 in paediatrics should be pooled together with PK data (IV and SC) from adults for an analysis, assessing if the drug exposures from IV administration in JMML paediatrics are comparable with that from SC/IV administration in adults, supporting IV use in JMML. Such analysis may be conducted using popPK methodology.

MAH Response to CHMP Question 2

Celgene confirms that the Clinical Overview has been updated to include a discussion on azacitidine pharmacokinetics (PK) in myelodysplastic syndromes (MDS) and juvenile myelomonocytic leukemia (JMML) (see Sections 3.4.2 and 3.4.2.1). Minor editorial updates have also been included through the document, as well as some additional clarifications in Section 3.4.1 Efficacy, for accuracy. A version in track changes is included in this submission for ease of review.

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/m2 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).

Table 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)	0.6 (0.14)	167.48 (48.69)	
IV	2750 (1068)	1044 (285.7)	1025 (298.1)	0.36 (0.02)	146.7 (46.9)	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.

All subjects in Study AZA-JMML-001 have been treated via IV administration of azacytidine 75 mg/m2. Pharmacokinetic data from pediatric subjects included in Study AZA-JMML-001 (10 MDS and 18 JMML subjects) were pooled together and compared to PK data from the 6 adult subjects with MDS administered 75 mg/m2 azacitidine IV in Study AZA-2002-BA-002 to assess if azacitidine drug exposures from IV administration in pediatrics are comparable to IV administration in adults. Exposure of azacitidine (maximum observed plasma concentration [Cmax] and AUC from time zero to last time with detectable levels [AUC0-t]) was similar between adult and pediatric subjects after IV administration (refer to Table 2), supporting IV use of azacitidine in JMML subjects.

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

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)
Pediatric (MDS +JMML) (N = 28)	2841 (4537)	882.1 (1421)	700.7[a] (1215)	0.379[a] (0.196)	192.9[a] (178.4)	102.0[a] (91.8)
Adults (MDS) (N = 6)	2750 (1068)	1025 (298.1)	1044 (285.7)	0.36 (0.02)	146.7 (46.9)	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; JMML = juvenile myelomonocytic leukemia; MDS = myelodysplastic syndrome; $t_{½}$ = half-life in terminal phase; V_z = volume of distribution
[a] N = 26
Source: Clinical Study Report AZA-JMML-001; Clinical Study Report AZA-CSR-004.

CHMP comment:

The Applicant compared exposure via IV administration of a 75 mg/m^2 dose to paediatric MDS (n=10) and JMML patients (n=18) with that obtained upon IV administration of a 75 mg/ m^2 dose to adult patients with MDS (n=6). Based on the mean exposure in all paediatric patients, exposure appears comparable with that in adult patients to a reasonable extent (i.e. AUC_{0-t} 882.1 h.ng/ml in paediatric patients and 1025 h.ng/ml in adult patients, respectively). As expected, the C_{max} in paediatric patients following IV administration was higher (2841 ng/ml) than that in adult patients after SC administration (i.e. 750 ng/ml, see Vidaza SmPC).

Although exposure in the paediatric population was comparable for the whole (MDS and JMML) paediatric population, the geometric mean AUC_{inf} in JMML patients appeared lower than in paediatric MDS patients (240.2 vs 606.9 h.ng/ml, respectively). The cause for this different exposure is unknown but may be partly due the high PK variability and also appears related to the younger age of the patients included for JMML than for MDS (median age 2.4 and 13.3 years, respectively). The causality of such relationship with age however is unclear.

Overall, it can be concluded that exposure to azacitidine in paediatric patients 0-17 following IV administration of a 75 mg/ m^2 dose appears in the same range as that in adults following IV administration of the same dose. Considering the high F of 89%, exposure is expected to be also comparable to that obtained in adults after SC administration of a 75 mg/ m^2 dose.

Issue resolved.

3. The MAH is requested to provide a text proposal for the relevant sections of the SmPC describing the results of this study in a concise and informative manner.

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~~.

CHMP comment:

The sections for which text proposals are presented are agreed. Comments to the text proposals are made following each section and changes to the text are suggested in **bold** (addition) or ~~double strikethrough~~ (deletion).

☐ SmPC Section 4.2

[…]

Special populations

[…]

Paediatric population

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

[…]

CHMP comment:

The text is in line with the guideline on SmPC. The text is agreed.

☐ SmPC Section 4.8

[…]

Paediatric population

In Study AZA-JMML-001, 28 paediatric patients (1 month to less than 18 years of age) were treated with Vidaza for MDS (n = 10) or juvenile myelomonocytic leukaemia (JMML) (n = 18) (see section 5.1).

All 28 patients experienced at least 1 adverse event, ~~of which~~ **and 17 (**60.7%**) experienced at least 1** treatment-related **event**. The most commonly reported adverse events in the overall paediatric population were pyrexia, haematologic events including anaemia, thrombocytopenia and febrile neutropenia, and gastrointestinal events including constipation and vomiting.

~~No events leading to death, dose reduction or drug interruption were reported~~ **Three (3) subjects experienced a treatment emergent event leading to drug discontinuation (pyrexia, disease progression and abdominal pain)**.

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.

[…]

CHMP comment:

This section should list events that do occur and not those that do not. So instead of stating that there were no events leading to death, dose reduction or interruption, it should be stated that three (3) subjects experienced a treatment emergent event leading to drug discontinuation (pyrexia, disease progression and abdominal pain). Furthermore, a minor change to the second paragraph is proposed because of clarity.

(suggestions in bold and strikethrough)

☐ SmPC Section 5.1

[…]

Paediatric population

~~Safety and effectiveness in paediatric patients have not been established (see section 4.2).~~

Study AZA-JMML-001 was a Phase 2, international, multicentre, open-label study to evaluate the pharmacokinetics, pharmacodynamics, safety and activity of Vidaza prior to HSCT in ~~a total of 28~~ paediatric patients (~~1 month to less than 18 years; 71% male~~) with newly diagnosed advanced MDS or JMML. **The primary objective of the clinical study was to evaluate the effect of Vidaza on response rate at Cycle 3, Day 28.**

Patients (MDS, n = 10; JMML, n = 18**; 3 month to 15 years; 71% male**) were treated with intravenous Vidaza 75 mg/m^2 **I.V**., daily on Days 1 to 7 of a 28-day cycle for a minimum of 3 cycles and a maximum of 6 cycles. ~~The primary objective of the clinical study was to evaluate the effect of Vidaza on response rate at Cycle 3, Day 28.~~

Enrolment in the MDS study arm was stopped after 10 MDS patients due to a lack of efficacy**: no confirmed responses were recorded in these 10 patients**.

In JMML study arm, 18 patients (13 *PTPN11*, 3 *NRAS*, 1 *KRAS* somatic mutations and 1 clinical diagnosis of neurofibromatosis type 1 [*NF-1*]) were enrolled. Sixteen patients completed 3 cycles of therapy and 5 of them completed 6 cycles. A total of 11 JMML patients had a clinical response at Cycle 3, Day 28, **of these 11 subjects, 9 (50%) subjects had a confirmed clinical response (3 subjects with cCR and 6 subjects with cPR)**. ~~The efficacy of Vidaza in these JMML patients was compared to an external historical registry control (n = 44) using a matched analysis, matched for the two most important prognostic factors, age (less than 7 years) and platelet count (< 100 x 10^9/L).~~ Among the cohort of JMML patients treated with Vidaza, ~~there was a higher percentage of patients~~ **7** (43.8%) **patients had a** ~~with~~ sustained platelet response (counts ≥ 100 × 10^9/L)**,** ~~and a lower percentage of patients~~ **7**(43.8%) requir**ed**~~ing~~ transfusions at HSCT ~~versus the historical cohort (9.1% and 63.6%, respectively)~~. **All patients proceeded to HSCT.**

Because of the study design (small patient numbers and various confounding factors), it cannot be concluded from this study whether Vidaza prior to HSCT improves survival outcome in JMML patients.

See section 4.8 for safety information.

CHMP comment:

The first sentence can be removed as it contains superfluous information. It is proposed to first state the general design of the study and describe the enrolled patient population followed by the dosing. Information on the route of administration is relevant and thus added.

The basis for the statement on the lack of efficacy in MDS subjects should be provided.

The comparison with historical controls should be removed, while it is relevant to know that all patients proceeded to transplant as intended.

☐ SmPC Section 5.2

[…]

Special populations

[…]

Paediatric population

In Study AZA-JMML-001, pharmacokinetic analysis was determined from 10 MDS and 18 JMML paediatric patients on Day 7 of Cycle 1 (see section 5.1**). The median age (range) of the MDS patients was 13.3 (1.9-15) years and 2.1 (0.2-6.9) years for JMML patients.**

Following intravenous administration of a 75 mg/m^2 dose, Vidaza rapidly reached C_{max} within 0.083 hours in both MDS and JMML populations. The geometric mean C_{max} were 1797.5 and 1066.3 ng/mL, and the geometric mean $AUC_{0-\infty}$ were 606.9 and 240.2 ng·h/mL, for MDS and JMML patients, respectively. The geometric mean volume of distribution in MDS and JMML subjects were 103.9 and 61.1 L, respectively. It appeared that the total plasma exposure of Vidaza was higher in MDS subjects; however, moderate to high between-patient variability was noted for both AUC and C_{max}.

The geometric mean $t_{½}$ were 0.4 and 0.3 hours, and the geometric mean clearances were 166.4 and 148.3 L/h for MDS and JMML, respectively.

Pharmacokinetic data from Study AZA-JMML-001 was pooled together and compared to pharmacokinetic data from 6 adult subjects with MDS administered 75 mg/m^2 Vidaza intravenously in Study AZA-2002-BA-002. Mean C_{max} and AUC_{0-t} of Vidaza were similar between adult patients and paediatric patients after intravenous administration (2750 ng/ml versus 2841 ng/ml and 1025 ng·h/mL versus 882.1 ng·h/mL, respectively).

[…]

CHMP comment:

The proposed text is acceptable. The age of the included paediatric patients should be provided here as well, as indicated in the text above.

4. 2nd Request for Supplementary Information

Based on the data submitted, the MAH should address the following questions:

1. The SmPC should be amended in line with the comments provided by the CHMP.

MAH responses

Question 1:

The SmPC should be amended in line with the comments provided by the Rapporteur.

MAH Response to CHMP Question 1

The MAH has reviewed the SmPC changes proposed by the Rapporteur and would like to express agreement with all changes, with just one minor clarification under section 5.1.

Section 5.1

Rapporteur's proposal: *'All patients proceeded to HSCT'*.

MAH clarification: 17/18 patients proceeded to HSCT. The text could be updated to either state this, or be phrased as "all responding patients proceeded to HSCT".

Assessment of MAH response

It is correct that one patient did not receive HSCT. We agree with the MAHsfirst proposal, to replace 'all patients proceeded to HSCT' by '17/18 patients proceeded to HSCT'.

5. Overall conclusion and recommendation

The benefit-risk balance for the studied paediatric populations cannot be determined due to uncertainties on the clinical relevance of the observed effect which are caused by the study design. However, the data obtained in the current study are considered of interest to the physicians treating children with MDS and/or JMML. As this concerns a paediatric population, results were proposed to be included in the SmPC. Thus, text proposal for the relevant sections in the SmPC are generally acceptable provided that the suggested changes are implemented.

The benefit-risk for the approved indications remains unchanged.

☒ **Fulfilled**