European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/593162/2008

ASSESSMENT REPORT
FOR
VIDAZA

International Nonproprietary Name:
azacitidine

Procedure No. EMEA/H/C/000978

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

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Pharmion Ltd. submitted on 09 January 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Vidaza. On the 23 July 2008, the application for Vidaza was transferred to Celgene Europe Ltd following the acquisition of Pharmion Corporation by Celgene Corporation.

Vidaza was designated as an orphan medicinal product EU/3/01/084 on 06 February 2002 in the following indication: treatment of myelodysplastic syndromes (MDS). The calculated prevalence of this condition was approximately 1.1 to 3 in 10,000 persons in EU population. At the time of orphan medicine designation, CMML was classified as a type of MDS.

Vidaza was also designated as an orphan medicinal product EU/3/07/509 on 29 November 2007 in the following indication: treatment of acute myeloid leukaemia (AML). The calculated prevalence of this condition was approximately less than 2 in 10,000 persons in EU population.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study (ies).

The applicant applied for the following indication: treatment of patients who are not eligible for haematopoietic stem cell transplantation with:

- Intermediate-2 and High-risk Myelodysplastic Syndromes (MDS) according to the International Prognostic Scoring System (IPSS),
- Chronic Myelomonocytic Leukemia (CMMoL (10%-29% marrow blasts without Myeloproliferative Disorder)),
- Acute Myeloid Leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) Classification.

Similarity
Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application contained a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol Assistance
The applicant did not seek Protocol Assistance at the CHMP.

Licensing status
Vidaza has been given a Marketing Authorisation in the following countryies on date:
United States of America (19.5.2004), Switzerland (24/02/2006), Israel (09.07.2006), The Philippines (21.09.2006), Hong Kong (25.03.2007), Thailand (10.10.2007), Turkey (10.10.2007), Argentina (09.11.2007), South Korea (27.01.2006)

A new application was filed in the following countries: South Africa, Egypt, Taiwan, Brazil and Australia.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Barbara van Zwieten-Boot Co-Rapporteur: Gonzalo Calvo Rojas

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 09 January 2008.
- Accelerated Assessment procedure was agreed-upon by CHMP on 24 January 2008.
- The procedure started on 30 January 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 April 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 April 2008.
- During the meeting on 27-30 May 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 30 May 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2008.
- The summary report of the inspection carried out at the following site: Ben Venue Laboratories, Inc. between 14-18 April 2008 was issued on 19 August 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 September 2008.
- During the CHMP meeting on 22-25 September, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 29 September 2008.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 10 October 2008.
- During the meeting on 20-23 October, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Vidaza on 23 October. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 October 2008.
- The CHMP adopted a report on similarity of Vidaza with Glivec and Trisenox on date 23 October 2008.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 17 December 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

MDS (myelodysplastic syndrome) is a rare and life threatening disease that can affect children and adults, although the highest prevalence occurs in those over 60 years of age.(1) The incidence of MDS has been estimated as 4.1/100,000 population. The incidence rises with increasing age: 4.9 for people aged 50 to 70 years and 22.8 for people older than 70 years.(1)

MDS encompasses a group of haematological disorders that is characterised by clonal haematopoietic stem cell disorder, usually of the granulocytic, erythroid or platelet lineage, that results in abnormalities in proliferation, differentiation and maturation of the myeloid lineage.(2) This leads to one or more peripheral cytopenias and progressive bone marrow failure. As a result, patients with MDS are at risk for symptomatic anaemia, infection and bleeding.(3)

The clinical presentation of MDS is generally non-specific. However, initial findings of MDS can usually be attributed to the underlying cytopenias. MDS can arise *de novo* (primary MDS) or following treatment with chemotherapy, radiation therapy or chemical injury (secondary MDS). Depending on the subtype of myelodysplasia, there is a risk of approximately 50% for development of acute myeloid leukaemia (AML), which is often refractory to standard treatment.

The diagnosis and classification of MDS can be based on two classification systems, the French-American-British (FAB) classification system and the more recent updated WHO classification system (4) (table 1).

Table 1 FAB and WHO classification systems for MDS

FAB	Blast count in bone marrow	Blast count in peripheral blood	WHO
Refractory anaemia (RA)	< 5%	≤ 1%	Refractory anaemia (RA)
	< 5%	≤ 1%	del(5q) syndrome
Refractory Anaemia with Ringed Sideroblasts (RARS)	< 5% with 15% ringed sideroblasts	≤ 1%	Refractory Anaemia with Ringed Sideroblasts (RARS)
	< 5%		Refractory Cytopenia with Multilineage Dysplasia (RCMD)
Refractory Anaemia with Excess Blasts (RAEB)	5-20	< 5	Refractory anaemia with excess blasts-1 (RAEB-1)
			Refractory Cytopenia with Multilineage Dysplasia and Ringed Sideroblasts (RCMD-RS)
	10-19		Refractory Anaemia with Excess Blasts-2 (RAEB-2)
Refractory Anaemia with Excess Blasts in Transformation (RAEB-T)	21-30	> 5	AML with multilineage dysplasia
AML	> 30		AML
Chronic MyeloMonocytic Leukaemia (CMMoL)	≤ 20	< 5	Myelodysplastic (WBC< $12x10^9$/l) Myeloproliferative disease (WBC > $12x10^9$/l)

The International Prognostic Scoring System issued in 1997 provides a method for evaluating clinical prognostic risk factors for patients with MDS (5). The 3 critical factors include risk-based cytogenetic subgroups (good, intermediate, and poor), bone marrow blast percentage and cytopenias. Patients are grouped into 4 risk categories based on total scores from these prognostic factors (table 2) (1, 3).

Table 2 IPSS for MDS - Prognostic risk based survival and AML evolution

	Total Score Value			
	0	0.5-1.0	1.5-2.0	≥ 2.5
Clinical outcome	Low	Intermediate-1	Intermediate-2	High
Overall Survival (median in years)	5.7	3.5	1.2	0.4
25% AML evolution (median in years)	9.4	3.3	1.1	0.2

Total Score Value is determined based on the combination of individual score of bone marrow blasts, karyotype and cytopenia

Despite current treatment strategies, approximately half of the patient population with MDS dies within 4 years. Cure may be achieved only in patients who can receive allogeneic haematopoietic stem cell transplantation (allo HSCT) (5). However, depending on a patient's age and general health condition, best supportive care (BSC), consisting in transfusions, growth factors, iron chelation therapy, is most frequently applied. Otherwise, low-dose chemotherapy or standard combination chemotherapy may be used for the various subclasses of MDS but without a standard approach of care (6). Only intensive chemotherapy followed by allo HSCT was shown to result in improved survival in patients with Intermediate-2 or high risk MDS or AML that progressed from MDS (AML-MDS) when compared with non-intensive treatment or supportive care only (actuarial survival at 4 years of 26% vs. 10%)(7, 8).

AML evolving from MDS is often less responsive to standard treatment than *de novo* AML. The usually higher age at diagnosis makes these patients more vulnerable to toxic effects from induction and consolidation chemotherapy (with e.g., cytarabine, etoposide and idarubicin) and the HSCT.

Vidaza, 5-azacitidine (azacitidine or 5-aza) is a pyrimidine nucleoside analogue of cytidine, a constituent of RNA. Due to its similarity to cytidine, azacitidine blocks the synthesis of DNA and RNA and thus inhibits the growth of tumour cells. Metabolites such as azacitidine are also associated with inhibition of DNA-methylation (hypomethylation) and can inhibit tumour growth (9). High-risk MDS shows a high prevalence of tumour suppressor gene hypermethylation, which induces inactivation of tumour suppressor genes. By re-establishing cell cycle control by restoring suppressor gene function and antiproliferative signals, this could contribute to re-establish cell differentiation pathways required for appropriate cellular function.

The marketing authorisation application for Vidaza was for the following indication: "Vidaza is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

– intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS),

– 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."

The recommended dose is 75 mg/m^2 s.c. once daily for 7 days every 28 days. The drug can be administered in an outpatient setting and is considered to be a low intensity form of therapy.

2.2 Quality aspects

Introduction

Vidaza is presented as a sterile, single use powder for suspension for injection containing 100 mg of azacitidine. It must be reconstituted with water for injections before subcutaneous injection.

The other ingredients include mannitol.

The finished product is packed in glass vials closed by a butyl rubber stopper and an aluminium seal with a plastic button.

- Active Substance

The active substance is azacitidine, a pyrimidine nucleoside analogue of cytidine.

It is a white to off-white solid, sparingly soluble in water. Azacitidine contains 4 chiral centres but it is synthesised as a single enantiomer. It is not hygroscopic but it hydrolyses quickly in water (reaction pH and temperature dependent). 9 solid-state forms have been identified: five polymorphic forms, three pseudopolymorphic forms and an amorphous form. Even if the active substance is fully solubilised during manufacture of the finished product, polymorphism could be of importance since the speed of dissolution of azacitidine could affect its degradation. However, all the polymorphs have been shown to convert quickly a single bioavailable pseudopolymorphic form in presence of water via rapid surface hydration and therefore in this case the physical form of the active substance is not expected to impact either on the stability or on the performance of the finished product.

- Manufacture

The manufacture of azacitidine comprises 4 main steps. All manufacturing steps have been well described.

The finalised specifications for starting material 5-azacytosine are considered to be adequate. There are no intermediates isolated in purified form in the manufacturing process. There are few process related impurities, monoacetyl azacitidine is detectable in the active substance.

- Specification

The active substance specification include tests for colour, appearance, identity (IR), optical rotation (PhEur), assay (HPLC), impurities (HPLC), residual solvents (GC), sulphated ash (PhEur), heavy metals (PhEur), water content (PhEur), microbial limits (PhEur) and bacterial endotoxins (PhEur).

Satisfactory batch analysis data have been provided to confirm compliance and uniformity with the proposed specification.

Impurity levels have been qualified by relevant toxicological studies.

- Stability

Stability data have been provided for 5 batches at accelerated conditions (25±2°C/60% RH) and long-term conditions (5±3°) respectively. 6-month and 4-year data have been provided. The parameters tested included colour, appearance, assay, related substances, water content and microbial limits testing. Analytical methods used in stability testing include water content (PhEur), microbial limits (PhEur.), assay (HPLC) and related substances (HPLC). An evaluation of polymorphic stability was also performed on active substance through 48 months under long-term storage conditions and through 6 months under accelerated storage conditions. The data demonstrated that no changes in polymorphic form were observed under any of the conditions studied for the duration of the evaluation

The applicant claims a re-test period of 3 years, if stored in double polyethylene bags secured in HDPE kegs at 2-8°C. No significant changes have been observed among the available stability results; no signs of degradation have been noticed. The claimed re-test period can be accepted.

- Pharmaceutical development

The proposed medicinal product is a powder for suspension for injection, a sterile, single-use drug formulation containing 100 mg azacitidine intended for reconstitution with 4 ml sterile water for injection to form a suspension prior to subcutaneous injection.

Azacitidine rapidly degrades in aqueous solution via hydrolysis. Due to this instability, an aqueous formulation was not a viable option. Thus, a lyophilized dosage form was developed to minimize water activity in the medicinal product.

Mannitol, used as a bulking agent for the lyophilisation process, is the only excipient in the formulation. It is of PhEur quality and its compatibility with azacitidine has been confirmed by development and long-term stability studies. There is no need to buffer the formulation as the active is not a salt and it remains uncharged at the pH of the sterile water for injections used to reconstitute the product. Regarding the TSE risk, the medicinal product does not include any components of ruminant origin.

To minimize azacitidine degradation during product manufacturing, the manufacturing process was developed such that compounding, filtration and filling operations are performed as a continuous process at reduced temperatures.

The type I glass vials and the siliconized rubber stopper used as primary packaging material meet the PhEur requirements. They are compatible with the product and capable to protect it from excessive moisture in relation to the proposed specification. Acceptable closure integrity studies (dye penetration and microbial challenge studies) have been performed.

- Manufacture of the Product

There are two manufacturers.

The manufacturing process involves the following operations: compounding, sterile filtration, aseptic filling, lyophilisation and packaging. A manufacturing overage for azacitidine was included to account for an observed loss of the compound during filtration.

Due to the instability of azacitidine in aqueous solution, control of product temperature throughout compounding, filtration, and filling and holding time are considered critical in order to minimize drug degradation.

The rapid freeze-drying applied leads to the formation of different polymorphs in the finished product. However, this has been found acceptable as it does not impact significantly either on the stability or on the performance of the finished product (see active substance). Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. The maximum holding time has been adequately justified based on azacitidine degradation data and microbiological data. Furthermore, manufacturing at reduced temperatures minimizes the risk of increasing bioburden over the short time interval.

Satisfactory validation data have been provided.

- Product specification

The finished product specification includes tests for colour, appearance, foreign matter, identity (Ph Eur), assay (HPLC), uniformity of dosage units (HPLC), impurities (HPLC), water content (PhEur), sterility (PhEur), bacterial endotoxins (PhEur) and colour and appearance of the reconstituted product.

Batch analysis data provided comply with the specifications and indicate consistent and reproducible manufacture.

- Stability of the product

Stability of the Product before reconstitution

Three batches of lyophilized powder from each of the manufacturers have been stored for up to 4 years (depending upon the manufacturing site), 1 year at 25°C/60% RH and 30°C/65% RH and for 6 months at 40°C/75% RH.

All of the testing results are well within specification for product stored under both accelerated and long-term storage conditions. The results presented support the proposed shelf life and storage conditions defined in the SPC for the finished product before and after reconstitution.

In-use stability of the reconstituted solution

The chemical and physical in-use stability of the reconstituted medicinal product of NMT 45 min at 25°C and NMT 8 hours at 2-8°C is accepted.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised and documented. The pharmaceutical form selected is adequate taken into account the properties and the stability of the active substance. The excipient is commonly used for this kind of formulation and the packaging material is well documented. The manufacturing process obtains reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.

At the time of the CHMP opinion there were some minor unresolved quality issues which had no impact on the benefit/risk profile.

2.3 Non-clinical aspects

Introduction

The non-clinical data are based on bibliographical information, applicant-sponsored studies and NCI-sponsored studies. Most of the non-clinical studies were conducted in the 1960s and 1970s before the introduction of Good Laboratory Practice (GLP) regulations and International Conference on Harmonisation (ICH) guidelines.

Pharmacology

- Primary pharmacodynamics

As a pyrimidine nucleoside analogue designed to incorporate into RNA and DNA instead of cytidine, azacitidine has a broad spectrum of anti-metabolic effects. The primary pharmacodynamic effects of interest in the treatment of MDS are:

- inhibition of DNA methylation.

- cytotoxicity by incorporation of azacitidine into DNA and RNA and inhibition of protein synthesis.

The concentration of azacitidine required for maximum inhibition of DNA methylation *in vitro* does not cause major suppression of DNA synthesis (10).

- Secondary pharmacodynamics

No secondary pharmacodynamic studies have been submitted.

- Safety pharmacology programme

No safety pharmacology studies have been submitted.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been submitted.

Pharmacokinetics

Most of the non-clinical pharmacokinetic studies of azacitidine were conducted in the 1960s using non-specific analytical methods available at that time. Through a programme designed to assess the oral (p.o.) route, recent pharmacokinetic data have been generated in 2 animal models: in mice, following radiolabelled azacitidine administered p.o and i.v. and in dogs treated with i.v., s.c. and p.o. azacitidine.

- Analytical methods

The concentration of azacitidine in biological samples from animal studies were determined by microbiological and/or radioisotope assays.

Microbiological assays were conducted with *Escherichia col*i grown on plates. A standard curve was developed to plot the inhibitory effect against azacitidine concentration. The concentration/response curve was linear between the concentrations of 3.12 and 25 µg/ml and the lowest detectable concentration was 2 µg/ml. The limit of assay sensitivity was 0.11 µg/ml of mouse blood. Azacitidine was not detectable in solid tissues.

Tissue levels of azacitidine were measured in mice following ^{14}C-azacitidine administration. Azacitidine-associated radioactivity was expressed as CPM (counts per minute) of $^{14}CO_2$ released on combustion of 10 mg fresh tissue or 0.1 ml of blood. Tissue distribution in all major tissues, organs and biological fluids was determined using whole-body autoradiography. Tissue concentrations were interpolated from standard curves.

LC-MS/MS methods were developed and validated to detect azacitidine in phosphate buffered saline (PBS) over the concentration range 24.4-1220 ng/ml (0.1-5 µM) and in dog plasma over the concentration range of 1-1000 and 5-2000 ng/ml. The methods involved extraction of azacitidine from plasma samples with acetonitrile followed by LC-MS/MS analysis.

- Absorption

No well-designed study was conducted to evaluate absorption of azacitidine through the s.c. route in animal. In one study performed in dogs, partial bioavailability data were collected and the absolute p.o. bioavailability was approximately 67% compared with the s.c. bioavailability of approximately 71%. There were no consistent gender differences in the pharmacokinetics following p.o. administration. Systemic exposure increased with increasing dose with little evidence of accumulation following repeat administration. Table 3 provides a summary of the available pharmacokinetic data in mouse and dog.

Table 3 Pharmacokinetics in mice and dogs

Species	Route	Dose (mg/kg)	T_{max} (h)	C_{max} (ng/ml)	$T_{1/2}$ (h)	AUC_{all} (ng*h/ml)	% of dose eliminated in urine	Reference
Mouse	i.p.	9.5	0.25	1-2 µg/ml	—		—	22
		4.75	0.25	0.2-0.3 µg/ml				
Mouse	i.p.	~13.7	—	—			~60[c,d]	23
Mouse	i.p.	50	—	—	—		~47[c,e]	24
Mouse	i.v.	10	0.5	9652[c]	9.6 [c]	20594[c]	67.4[c,f]	25
	p.o.	50	0.5	24645[c]	10.0 [c]	38883[c]	60.5[c,f]	
Dog	p.o.	0.8[a]	0.67	580	—	810	—	26
		0.8[b]	1.2	550		740		
Dog	p.o.	0.2[a]	0.9	143	0.88	230	—	27
		0.4[a]	0.85	191	0.98	331		
		0.8[a]	0.75	652	0.78	1029		
		0.8[b]	1.05	726	0.84	1040		
Dog	i.v.	2	0.15	204		94		28, 29
	s.c.	2	0.67	85	—	67	—	
	p.o.	6	0.33	329		63		
Dog	i.v.	0.5	—	—	—		~33[c,g]	30

a Capsule administration (API filled)
b Enteric-coated tablet administration
c Radioactivity
d 24 hour; e 8 hour; f 48 hour; g 4 hour

- Distribution

The first tissue distribution study in AKR mice treated i.p. with ^{14}C-azacitidine showed that radioactivity declined sharply in blood during the first 8 hours but was still present 24 hours after dosing. Tissue radioactivity was determined in thymus, spleen, kidney, liver, brain, and muscle. Concentrations of radioactivity were higher and retention was longer in spleen and thymus than in other tissues. Concentrations in kidney and liver were significantly less than in lymphoid tissues and only small amounts of radioactivity were recorded in muscle and brain.

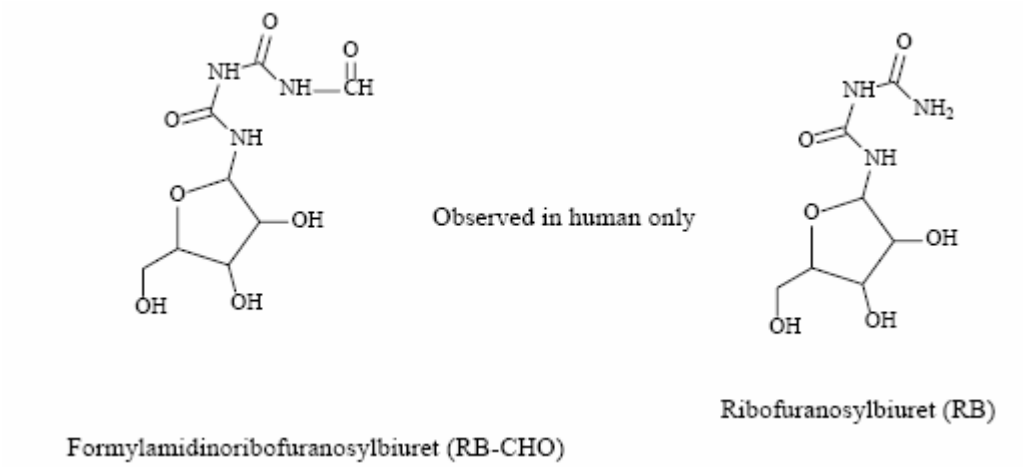
A recent tissue distribution study was conducted in ICR mice treated p.o. (50 mg/kg) or i.v. (10 mg/kg) with ^{14}C-azacitidine (25). Using whole body autoradiography, tissues were examined for radioactivity content at 0.5, 1, 3, 6, 24, and 48 hours after dosing. Radioactivity was widely distributed throughout all organs and tissues. Other than the excretory/metabolic tissues (which include kidney, liver, bile, gall bladder and urinary bladder) and the gastrointestinal system tissues, consequent levels of radioactivity were recovered in spleen, bone marrow, thymus, pancreas, adrenal gland, salivary gland, lacrimal gland, prostate/uterus, lung, diaphragm and myocardium. Most tissues showed maximal concentrations between 0.5 and 1 hour which declined steadily thereafter. At 48 hours, tissue concentrations of radioactivity were higher in i.v. treated animals than in those treated orally.

- Metabolism

Azacitidine is transported into the cell by the same facilitated nucleoside transport system as uridine and cytidine. Intracellular azacitidine undergoes 3 sequential phosphorylation reactions resulting in azacitidine triphosphate. The first phosphorylation reaction, the rate-limiting step in azacitidine metabolism, is mediated by the enzyme uridine-cytidine kinase (a.k.a. uridine kinase). This reaction is subject to feedback inhibition by either uridine triphosphate (UTP) or cytidine triphosphate (CTP).

Azacitidine triphosphate may then be incorporated into RNA and DNA resulting in the pharmacologic effects of demethylation and cytotoxicity.

Catabolism of azacitidine is by spontaneous hydrolysis and by deamination. Spontaneous hydrolysis of azacitidine results in equilibration with n-formylguanylribosylurea (RGU-CHO) culminating in the irreversible formation of guanylribosylurea (RGU). The labile hydrolysis product, RGU-CHO, has a biological activity approximately one-fourth of the potency of azacitidine. Although the RGU degradation product has not been completely characterised, it exhibited no pronounced toxicity using *in vivo* or *in vitro* test systems.



Incubation of [14C] 5-azacitidine with mouse hepatic S9 fractions yielded 2 products (RGU-CHO and RGU); incubation with human hepatic S9 fractions produced an additional two additional compounds identified as ribofuranosylbiuret and formylamidinoribofuranosylbiuret. The formation of metabolites was independent of NADPH and occurred at the same rate with either hepatic S9 or denaturated S9 preparations, implying that metabolism was catalysed by cytosolic enzymes.

The metabolic stability of azacitidine was evaluated in heat-treated and untreated intestinal tissue homogenates prepared from dog, pig and human. All segments from the dog, pig and human intestinal tissues exhibited esterase activities and showed that heat-treatment abolished or reduced such activities.

- Excretion

Limited data on the excretion of azacitidine in mice were presented in the paper by Raska et al. (23). Urinary excretion was studied in mice and dogs (table 3). In mice administered 14C-azacitidine i.p , approximately 45% of the radio-labelled compound was recovered in the urine. Moreover, recovery of 14C-azacitidine delivered by p.o. or i.v. routes of administration demonstrated that the majority of the excreted radioactivity was found in urine (60.5 ± 6.6% and 67±8.8% of the dose, respectively) and only a fraction of the dose was recovered in the faeces (17.2±4.5% and 1.3±0.6%, respectively). An attempt was made to characterise the major metabolites found in urine with HPLC, GC and MS. Six radioactive peaks were identified as summarised in table 4 (29).

Table 4 Urinary metabolites of ^{14}C azacitidine in mice

HPLC peak	Identity	% recovery[b]
I	5-azauracil	23.2 ± 5.4
II	Not characterised but maybe 5-azauridine	19.9 ± 6.0
III	5-azacytosine (maybe a contaminant)	4.6 ± 0.1
IV	Azacitidine (a.k.a. 5-azacytidine)	3.6 ± 2.0
V	Ribofuranosylbiuret	26.5 ± 5.0
VI	Multiple components partially characterised	19.1 ± 1.8

a Values represent the per cent recovery from the HPLC column (mean ± SD). The per cent of the total dose recovered in the urine was 45.0 ± 10.9

A urinary metabolic profiling study was also performed with ^{14}C-azacitidine in dogs dosed at 0.5 mg/kg i.v.. Recovery of radioactivity in urine during the 4-hour interval after dosing represented 33% of the dose (30). The same 6 HPLC ^{14}C peaks that were present in mice were present in the dog.

- Pharmacokinetic drug interactions

The potential for azacitidine to inhibit human hepatic cytochrome P450 (CYP) enzymes has been evaluated. The following enzymes were used in the evaluation: CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Azacitidine was not found to inhibit isozymes CYP2C9, CYP2C19, CYP2D6 and CYP3A4 at a maximal concentration of 100 μM (30-fold higher than clinically achievable plasma concentration of azacitidine following the recommended dose), although a low to moderate inhibition of CYP1A2 and 2E1 was observed. In addition, the effects of azacitidine on the expression of cytochrome P450 were evaluated. Cultures of human hepatocytes were exposed to azacitidine at various concentrations for 72 h. Treatment of human hepatocytes with azacitidine did not cause increased activity in CYP1A2, CYP2C19 and CYP3A4/5 but an unexpected inhibitory effect on 3A4/5 activity was observed at 100 μM. The inhibitory effect was thought to be due to CYP 3A4/5 protein suppression.

Toxicology

Toxicology data were collected from *in vitro* studies and *in vivo* studies conducted in mice, rats, dogs, and rhesus monkeys. The studies are detailed in table 5.

Table 5 Toxicology programme

Study type and duration	Route of administration	Species or test system	Reference
Single-dose toxicity	p.o., i.p. and i.v.	Mouse	31-33
	i.v.	Rat and dog	
Repeat-dose toxicity			34-38
2 days	p.o.,	Dog	
5 days	p.o., i.p. and i.v.	Mouse	
5 days and 5 days in 2 cycles	i.v.	Dog	
14 days	i.v.	Monkey	
14 days	p.o.	Dog	
Genotoxicity	*In vitro*	*Salmonella typhimurium*	39-48
		Escherichia coli	
		Human lymphoblast cells	
		Mouse lymphoma cells	
		Mouse leukaemia	
		Hamster embryo cells	
Carcinogenicity			49-51
50 and 52 weeks	i.p.	Mouse	
9-18 months and 34 weeks	i.p.	Rat	
Reproductive and developmental toxicity	i.p.	Mouse and rat	52-59
Local tolerance	Dermal cheek pouch	Rabbit	60-61
		Hamster	
Antigenicity	s.c.	Guinea pig	n/a

- Single dose toxicity

Single dose toxicity studies were conducted in mice (oral, i.p., i.v.), rats (i.v.) and dogs (i.v.). The main results are summarised in table 6.

Table 6 Single dose toxicity main results

Study ID	Species/ Number per sex and group	Dose (mg/kg)/Route	Approx. lethal dose/observed max non-lethal dose (mg/kg)	Major findings
Palm 1970	Swiss mice/10	0, 431, 519, 624, 750 oral (gavage)	LD_{10} 455 LD_{50} 572 LD_{90} 750 Non-lethal dose < 431	> 431: ↓ weight gain > 519: ↓ liver glycog. Toxicity in males > females Mean time of death was day 4
Palm 1970	Swiss mice/10	0, 79.2, 99.7, 125.6, 158.1 i.p.	LD_{10} 89 LD_{50} 116 LD_{90} 146 Non-lethal dose 79.2	≥ 99.7: ↓ weight gain Degeneration of kidney tubules and hepatocytes Toxicity in males > females Mean time of death was day 4
Palm 1973	Swiss mice/10	0, 62.9, 79.2, 99.7, 125.6, 158.1 i.v. (PVP formulation)	LD_{10} 87 LD_{50} 117 LD_{90} 172 Non-lethal dose 79.2	≥ 79.2: ↓ weight gain ≥ 62.9: extramedullary heamtopoiesis (spleen) Mean time of death was day 6
Reno 1983 (US GLP)	$CD2F_1$ mice /10	0, 150, 173, 199, 229, 264, 304, 350 i.v. (Lactated Ringer's)	LD_{10} 199 LD_{50} 250 LD_{90} 313 Non-lethal dose 150	≥ 173 ↓ weight gain ♀ ≥ 264 ↓ weight gain ♂ Deaths occurred days 3-11
Palm 1973	SD rats/10	0, 41, 46.1, 51.7, 58, 65.1 i.v. (PVP formulation)	LD_{10} ≈38.5 LD_{50} 51.4 LD_{90} ≈64.5 Non-lethal dose 41	≥ 46.1: ↓ weight gain ≥ 51.7: ↑ hepatic lipid 92% of deaths occurred by Day 6
Palm 1970	Beagle dogs/ one animal per dose (2F+1M)	3.32, 6.65, 13.2 i.v.	13.2 Non-lethal dose 6.65	≥ 3.32: ↓ WBC, ↑ SGPT 13.2: moribund, sacrifice on Day 2 Severe weight loss ↑ BUN. SGOT, SGPT Degenerative changes in bone marrow, lymphatic tissues, kidney, and liver

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies were performed in mice (p.o., i.p., i.v.), dogs (i.v.) and monkeys (i.v.). The main results of the repeat-dose toxicity studies are displayed in table 7.

Table 7 Repeat-dose toxicity main results

Study ID	Species/Number per sex and group	Dose (mg/kg)/Route	Duration	NOAEL (mg/kg)	Major findings
Palm 1970 Non-GLP	Swiss mice/10	0, 3, 4.16, 5.04, 6 Oral (gavage)	5 days	≈3 (LD_{50} 4.35)	> 3: ↓ body weight at Day 8 Mean time to death: Day 16
Palm 1970 Non-GLP	Swiss mice/10	0, 1.1, 1.61, 2.35, 3.42, 5 i.p.	5 days	< 1.1 (LD_{50} 2.48)	≥1.1: ↓body weight at Day 8 Mean time to death: Day 13
Reno 1983 (US GLP)	$CD2F_1$ mice/15	0, 6.5, 8.2, 10.4, 13.2, 16.2, 21.2, 26.8 i.v. (Lactated Ringer's)	5 days	< 6.5 (LD_{50} 12.9)	≥ 6.5: ↓body weight Most deaths occurred Days 4-12
Palm 1970 Non-GLP	Beagle dogs/1	0.28, 0.55, 1.1, 2.2, 4.4 i.v.	5 days	0.28	0.55: ↓ WBC & RBC ≥ 1.1: ↑ SGPT ≥ 2.2: ↑ BUN 4.4: both died on Day 4
Palm 1970 Non-GLP	Beagle dogs/1	0, 0.28, 0.55, 1.1 i.v.	5 days x 2 cycles	0.28	0.28: ↑ WBC (one dog) 0.55: ↓ WBC, ↑ SGPT 1.1: 1M died on Day 15
Palm 1971 Non-GLP	Beagle dogs/1 (for each formulation)	0, 0.55 i.v. (PVP vs. water)	5 days x 2 cycles	< 0.55	↑ SGPT & BUN ↓ RBC No difference water-PVP
Popke, 2007 GLP	Beagle dogs/5	0, 0.2, 0.4, 0.8 p.o.	14 days	0.2	p.o. ≥ 0.4 mg/kg/day → ↑ mortality, severe pancytopenia, cellular depletion in the bone marrow, and lymphoid depletion in the thymus, spleen, and lymph nodes
Palm 1972 GLP	Rhesus monkey/1	0 (water), 0 (PVP), 0.28, 0.55, 1.1, 2.2 i.v. (5-aza in PVP)	14 days	< 0.28	≥ 0.28: ↓ WBC ≥ 1.1: Bone marrow hypoplasia Liver fatty metamorphosis 2:2: ↑ SGOT, SGPT & BUN

Toxicokinetics was investigated in one 14-day toxicity study in dogs. Results of the toxicokinetic modelling are summarised in table 8. Systemic exposure increased with increasing dose but accumulation of azacitidine following repeated administration was not observed.

Table 8 Toxicokinetic results in dogs in 14-day toxicity study

Parameters	0.2 mg/kg[a]		0.4 mg/kg[a]		0.8 mg/kg[a]		5 mg/dog/day[b]	
	Male	Female	Male	Female	Male	Female	Male	Female
Day 1								
C_{max} (ng/ml)	119	168	175	207	721	583	657	795
T_{max} (hr)	0.903	0.900	0.800	0.907	0.817	0.703	1.10	1.01
AUC_T (hr·ng/ml)	178	237	269	306	1040	907	932	1000
AUC (hr·ng/ml)	222	273	319	342	1090	967	1000	1080
$T_{1/2}$ (hr)	0.977	0.782	1.10	0.862	0.767	0.781	0.836	0.844
Day 10 (0.8 mg/kg/day and 5mg/anumal/day) or Day 14 (0.2 mg/kg/day and 0.4 mg/kg/day)								
C_{max} (ng/ml)	129	152	251	313	880	761	1080	744
T_{max} (hr)	0.600	0.703	0.803	0.707	0.600	0.746	1.13	1.13
AUC_T (hr·ng/ml)	148	223	344	478	997	971	756	823
AUC (hr·ng/ml)	168	239	362	501	1320	1330	885	1170
$T_{1/2}$ (hr)	0.821	0.993	0.792	0.883	0.829	0.843	0.709	0.837

a administered as a capsule (API filled)
b targeted 0.8-mg/kg/day dose administered as a fixed 5-mg/animal/day enteric-coated tablet

The relative sensitivity of various animal species to azacitidine from selected studies is presented in table 9.

Table 9 Species sensitivity to azacitidine

Species	Route	Duration	Maximum tolerated dose[a]	Lethal dose
Mouse	i.p.	Single dose	< 89 mg/kg (267 mg/m^2)	> 89 mg/kg (267 mg/m^2)
Mouse	i.v.	Single dose	63 mg/kg (189 mg/m^2)	79 mg/kg (237 mg/m^2)
Mouse	i.v.	5-days	6.5 mg/kg (19.5 mg/m^2)	11.3 mg/kg (33.9 mg/m^2)
Rat	i.v.	Single dose	~ 38 mg/kg (228 mg/m^2)	41 mg/kg (246 mg/m^2)
Dog	i.v.	Single dose	6.65 mg/kg (133 mg/m^2)	13.2 mg/kg (264 mg/m^2)
Dog	i.v.	5 days	2.2 mg/kg (44 mg/m^2)	4.4 mg/kg (88 mg/m^2)
Dog	i.v.	5-days x 2 cycles	0.55 mg/kg (11 mg/m^2)	1.1 mg/kg (22 mg/m^2)
Dog	p.o.	14 days	0.2 mg/kg (4.0 mg/m^2)	0.4 mg/kg (8.0 mg/m^2)
Monkey	i.v.	14 days	1.1 mg/kg (16.0 mg/m^2)	2.2 mg/kg (32.0 mg/m^2)

a Conversions from mg/kg to mg/m^2 were based on approximate human and animal weights using a web-based Oncology Tools dose calculator. The doses in mg/kg for mouse, rat, dog, and monkey were multiplied by 3, 6, 20, and 14.5, respectively to obtain the corresponding dose in mg/m^2

- Genotoxicity

A number of genotoxicity studies have been submitted in the format of bibliographical references (12, 18, 39-48). Azacitidine had both mutagenic and clastogenic activity in several bacterial and mammalian cell systems under the conditions tested.

- Carcinogenicity

Four of carcinogenicity studies have been submitted in the format of bibliographical references (49-51). Azacitidine has carcinogenic potential in rodents capable of inducing tumours in a variety of organs (lymphoid system, lung, mammary gland, and skin).

- Reproduction toxicity

A number of reproductive and developmental toxicity studies in mice (i.p.) and rats (i.p.) have been submitted in the format of bibliographical references (13, 19, 52-59). Azacitidine was associated with significant risk to the embryo, foetus and male reproduction system. The reproductive and developmental toxicity of azacitidine results from the cytotoxicity to rapidly dividing cells (S-phase) and alterations in gene expression. Spermatogenesis in rats is at risk because of the high level of cell proliferation. In embryofoetal development studies, azacitidine caused dose-dependant embryotoxicity and teratogenicity at doses as low as 0.3-0.5 mg/kg (or 3 to 6 mg/m^2). Higher doses increased the incidence of foetal malformations and embryolethality.

- Local tolerance

Local tolerance studies were conducted.

- Other toxicity studies

None submitted

Ecotoxicity/environmental risk assessment

The majority of azacitidine given subcutaneously is excreted in the urine. The amount of azacitidine and its metabolites reaching the environment as a result of the administration of azacitidine powder for suspension for injection is not considered to be sufficient to significantly change the quality of the human environment. As azacitidine is highly water soluble and the octanol/water partition coefficient (log Ko/w) is less than 0.5 over a pH range of 2-12, the compound is most likely to amass predominantly in the aquatic environment. Emission patterns will consist mainly of a diffuse release into waste water systems due to excretion of the active substance and/or its metabolites by patients. Additional data on the ERA will be provided as a follow up measure.

Discussion on the non-clinical aspects

Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non-proliferating cells are relatively insensitive to azacitidine. Incorporation of azacitidine

into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation and death pathways may result in gene re-expression and restoration of cancer-suppressing functions to cancer cells. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of azacitidine to clinical outcomes has not been established.

No secondary pharmacodynamic studies have been submitted. These are well known and described in the literature. Azacitidine has also immunosuppressive, antimicrobial, genotoxic, embryotoxic, teratogenic and carcinogenic effects (11-20). These secondary effects are in common with the pharmacologic activity of other pyrimidine analogues used as antiviral and antineoplastic agents (21). The absence of additional studies is considered acceptable.

The Applicant has provided sufficient justification for the absence of specific safety pharmacology data. Therefore due to the abundance of clinical data together with the data from the dog toxicity study this omission is accepted.

No pharmacodynamic drug interactions studies were submitted. This is acceptable in view of the monotherapy indication. Concurrent administration of azacitidine with other antineoplastic agents may affect the pharmacodynamics of either compound.

Systemic exposure increased with increasing dose with little evidence of accumulation following repeat administration. Radioactivity was widely distributed throughout all organs and tissues. Most tissues showed maximal concentrations between 0.5 and 1 hour which declined steadily thereafter. In mice, recovery of 14C-azacitidine delivered by p.o. or i.v. routes of administration demonstrated that the majority of the excreted radioactivity was found in urine (60.5 ± 6.6% and 67±8.8% of the dose, respectively) and only a fraction of the dose was recovered in the faeces.

No non-clinical toxicity studies were performed using the s.c. route, the intended route of administration in humans. Nevertheless, the results obtained from i.v. and i.p. administration are considered adequate to characterise the systemic toxicity of azacitidine taking into account the known toxic profile of azacitidine.

Azacitidine has both mutagenic and clastogenic activity. Azacitidine has carcinogenic potential. These findings are consistent with that of other nucleoside analogues.

Azacitidine was associated with significant risk to the embryo, foetus and male reproduction system. Azacitidine should not be administered to pregnant women or women of childbearing potential. These constraints should also apply to men being treated with azacitidine whose partners are of childbearing potential. These risks are adequately addressed in the SPC. MDS is a disease of the elderly and, therefore, no offspring study has been performed. This omission is acceptable.

Local tolerance studies were submitted. However, the findings from these studies were not relevant as none of these studies were conducted using the s.c. route of administration. Sufficient data are available from the toxicology studies and no further local tolerance studies are required.

As the clinical data appears to be sufficient to assess dependency, no applicant-sponsored animal studies have been conducted to assess the dependence potential of azacitidine.

While studies have been submitted to assess the degradation products of azacitidine, no toxicity studies specifically designed to assess toxicity of individual azacitidine metabolites have been submitted. However, individual impurities have each been limited to 0.15% w/w to correspond with the qualification threshold identified by ICH Guidance Q3A (R2).

The environmental risk assessment for azacitidine cannot be completed based on the assessment provided. The applicant committed to submit a phase II assessment as a follow-up measure.

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs); interactions related to these metabolizing enzymes *in vivo* are therefore considered unlikely. Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely (see SPC section 5.2). The applicant will conduct a new study to evaluate the interaction of azacitidine with CYP2B6 and CYP2C8 isozymes.

2.4 Clinical aspects

Introduction

The clinical development of azacitidine was initiated by the Cancer and Leukemia Group B (CALGB), and clinical results were published during the period 1989 to 2002. The main clinical study in this application is study AZA-001, an open-label, parallel-group, randomized, controlled phase 3 clinical trial (AZA-PH-GL-2003-CL-001 later named AZA-001). The CHMP granted an accelerated assessment procedure pursuant to Article 14 (9) of Regulation (EC) No 726/2004 for Vidaza on 24 January 2008, as the designation of an unmet medical need in the defined patient category was fulfilled (higher-risk-MDS incidence estimate 1-2/100,000). Based on the claims and description of the available data provided by the applicant, the product was considered to be of major public health interest from the viewpoint that it might provide a treatment option that could have supplementary value with regard to the present therapeutic arsenal for patients with MDS. However, due to major objections at D120, the application reverted to a normal timetable.

The proposed route of administration of azacitidine is subcutaneous, with a recommended starting dose for MDS patients of 75 mg/m^2 daily for 7 days every 4 weeks. Azacitidine can be administered in an outpatient setting and patients should be monitored for haematologic and renal toxicities as dosage adjustments may be necessary. The duration of clinical use may be greater than one year.

GCP

Some of the clinical trials were originally conducted under prior to implementation of ICH GCP guidelines. The AZA-PH-GL-2003-CL-001 study was stated to be performed in accordance with GCP.

Pharmacokinetics

The human pharmacokinetics of azacitidine was initially investigated in the 1970s following treatment of patients with the radiolabelled drug. More recently, study AZA-2002-BA-002, a multicentre, randomised, open-label crossover design in 6 MDS patients comparing the pharmacokinetics of single dose s.c. versus i.v. doses of azacitidine 75 mg/m^2. Additionally, a published report described the pharmacokinetics of s.c. administered azacitidine when given with phenylbutyrate (by i.v. infusion) (62). Supportive studies have also been conducted to assess azacitidine interaction with cytochrome P450 enzymes.

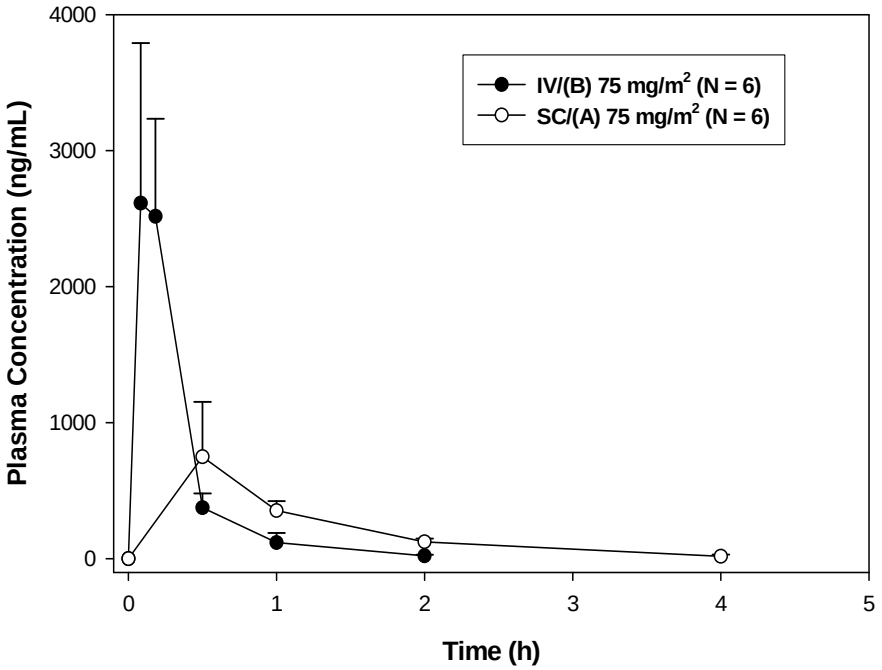
- Absorption

Bioavailability

In study AZA-2002-BA-002, azacitidine was administered to 6 MDS patients. Patients received either a single dose of 75 mg/m^2 administered either s.c. or i.v. over 10 minutes in a randomised 2-way crossover design.

The mean plasma concentration versus time curves for s.c. and i.v. administrations of azacitidine are shown in Figure 1 and pharmacokinetic parameters are summarised in table 10.

Figure 1 **Study AZA-2002-BA-002 - Mean plasma azacitidine concentration versus time in MDS patients**



Azacitidine was rapidly absorbed following s.c. administration with maximum plasma concentrations (C_{max}) of 750 ± 403 ng/ml occurring at the first post-dose sampling time (0.5 hour). Following i.v. infusion, C_{max} was seen after 5 minutes in 2 of 6 patients and at the end of saline flush (11 minutes) in the remaining 4 patients.

Table 10 **Study AZA-2002-BA-002 - Azacitidine pharmacokinetic parameters following s.c. and i.v. dose administration in MDS patients**

Route	C_{max} (ng/ml)	$AUC_{0\text{-}inf}$ (ng*h/ml)	t_{max} (h)	$t_{1/2}$ (h)	CL (l/h)	V_d (l)	F^1 (90% CI) (%)
s.c.	750 ± 403	960 ± 458	0.5 ± 0.0	0.69 ± 0.14	167 ± 49[1]	NA	89 (70-112)
i.v.	2750 ± 1089	1044 ± 286	0.15 ± 0.05	0.36 ± 0.02	147 ± 47	76 ± 26	NA

1 F = Absolute bioavailability based on AUC0-inf of the SC/IV ratio of the geometric LS means

Absolute bioavailability, based on $AUC_{0\text{-}inf}$ of the SC/IV ratio of the geometric least squares means was 89% (90% CI 70-112%).

- Distribution

Pharmacokinetics in study AZA-2002-BA-002 showed that the mean volume of distribution following i.v. dosing was 76 ± 26 l (0.99 ± 0.34 l/kg).

- Elimination

Excretion

Excretion of azacitidine and metabolites were characterised by radiotracer studies in patients with advanced cancer following both i.v. and s.c. administration (63, 64). Based on total radioactivity in plasma, which represented parent drug plus circulating metabolites, it was shown that kidneys excreted azacitidine and/or its metabolites, with 50 (s.c.) to 100% (i.v.) of the administered radioactivity recovered in the urine over 48 to 72 hours. Following i.v. administration, less than 1% was excreted in the faeces. The elimination half-lives in this study were similar (3.4-6.2 hours) for both modes of administration.

In study AZA-2002-BA-002, azacitidine was rapidly eliminated following either s.c. or i.v. administration. The mean half-life after i.v. administration was 0.36 hours, while that after s.c. administration was slightly longer (0.69 hours). The apparent (s.c.) clearance (167 l/h or 2791 ml/min) and systemic (i.v.) clearance (147 l/h) of azacitidine far exceeded literature values of glomerular

filtration rate (approximately 125 ml/min) and total renal blood flow (1200 ml/min) in healthy patients.

Metabolism

No *in vivo* metabolism studies were submitted.

Inter-conversion

Upon reconstitution of the azacitidine medicinal product the conformation of the product were found to convert to pseudopolymorphic Form III. Form III is the bioavailable form since it is always formed in water regardless of the original polymorphic form of the active substance or medicinal product.

Pharmacokinetics of metabolites

No studies on the pharmacokinetics of metabolites were submitted.

Consequences of possible genetic polymorphism

No data were submitted.

- Dose proportionality and time dependencies

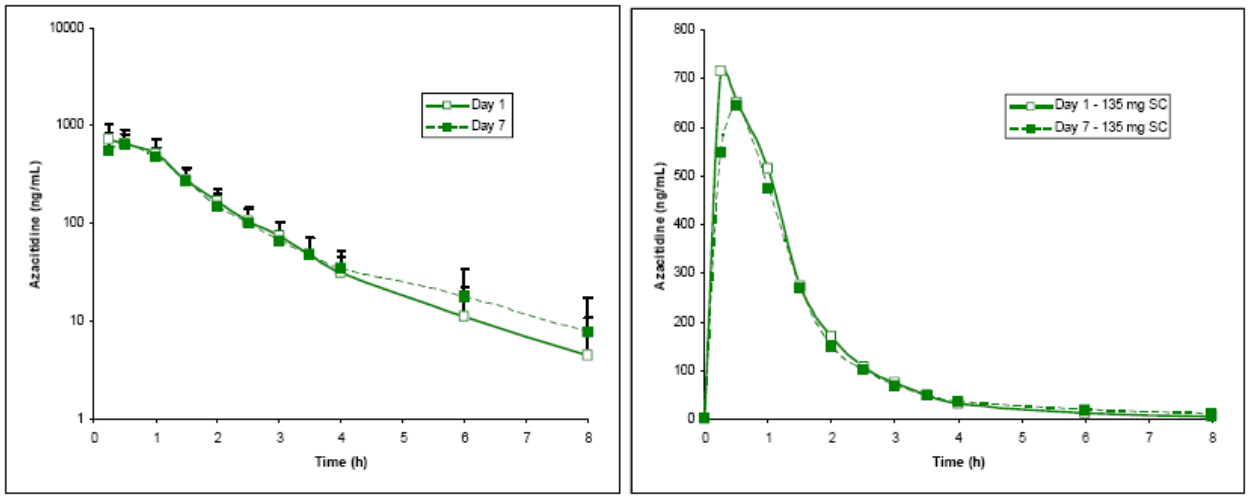
Dose proportionality

No studies on dose proportionality have been submitted. This will be addressed as a follow up measure.

Time dependency

Based on preliminary analyses, the plasma pharmacokinetic profile of azacitidine following 7 consecutive daily doses of azacitidine is essentially super-imposable upon the profile following single dose treatment, although there is some variability at very low concentrations in the tail end of the curves (see figure 2). The formal report will be submitted when completed.

Figure 2: Plasma concentration-time profiles (semi-logarithmic and linear scales) of azacitidine following subcutaneous treatment (75 mg/m^2)



- Special populations

Impaired renal function

The effects of renal impairment on the pharmacokinetics of azacitidine have not been studied. This will be addressed as a follow up measure.

Impaired hepatic function

The effects of hepatic impairment on the pharmacokinetics of azacitidine have not been studied.

Gender

Safety subgroup analyses did not reveal any clinically relevant differences between genders.

Race

More than 90% of the patients enrolled in the CALGB and AZA studies were Caucasian and, therefore, no safety subgroup analysis for race could be made.

Weight

The effects of weight on the pharmacokinetics of azacitidine have not been studied.

Elderly

The effects of age on the pharmacokinetics of azacitidine have not been studied. In the pivotal clinical Study AZA-001, a large proportion of patients was over 65 (84/179 > than 65; 38/179 > 75 years of age; maximum age, 88 years). Also in the earlier Studies CALGB 8921 and 9221, a large proportion of patients were > 75 years of age. Safety subgroup analyses did not reveal any clinically relevant differences between different age groups.

Children

The effects of age on the pharmacokinetics of azacitidine have not been studied.

- Pharmacokinetic interaction studies

Clinical drug interaction studies with azacitidine were not submitted.

In vitro experimental data indicate that azacitidine is not metabolised via CYPs, UGTs, SULTs and GSTs. Although, clinical interactions involving these major metabolism pathways are not expected, interaction of azacitidine with CYP2B6 and CYP2C8 will be addressed in future studies as a follow up measure.

Pharmacodynamics

No clinical pharmacodynamic studies have been submitted. A review of published non-clinical data was presented to demonstrate the effect of azacitidine on DNA methylation, gene expression and cell differentiation in normal and neoplastic cells.

The proposed dosage regimen of azacitidine, as used in the major studies supporting this MAA, was based on clinical results obtained in the studies CALGB 8421 and CALGB 8921. In the study CALGB 8421, it was demonstrated that azacitidine is active in the treatment of higher-risk MDS when given IV or SC at 75 mg/m^2/day for 7 consecutive days every 28 days. This dosage was initially based on the clinical experience earlier obtained with azacitidine at 140 mg/day, for the treatment of sickle cell anaemia and beta-thalassemia.

Discussion on clinical pharmacology

The pharmacokinetics of azacitidine were studied following single 75 mg/m^2 doses given by subcutaneous and intravenous administration.

Absorption

Azacitidine was rapidly absorbed after subcutaneous administration with peak plasma azacitidine concentrations of 750 ± 403 ng/ml occurring at 0.5 h (the first sampling point) after dosing. The absolute bioavailability of azacitidine after subcutaneous relative to intravenous administration was approximately 89 % based on area under the curve (AUC).

Distribution

Following intravenous administration, the mean volume of distribution was 76 ± 26 l, and systemic clearance was 147 ± 47 l/h.

Metabolism

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs).

Metabolism of azacitidine is by spontaneous hydrolysis and by deamination mediated by cytidine deaminase. In human liver S9 fractions, formation of metabolites was independent of NADPH implying any metabolism would be catalysed by cytosolic enzymes. *In vitro* studies of azacitidine with cultured human hepatocytes indicate that at concentrations of 1.0 μM to 100 μM (i.e. up to approximately 30-fold higher than clinically achievable concentrations), azacitidine does not induce cytochrome P450 isoenzymes (CYP) 1A2, 2C19, or 3A4 or 3A5. In a study to assess inhibition of a series of P450 isoenzymes (CYP 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) incubated with 100 μM azacitidine, IC_{50} values could not be determined, therefore, enzyme inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Excretion

Azacitidine is cleared rapidly from plasma with a mean elimination half-life ($t_{½}$) after subcutaneous administration of 41 ± 8 minutes. Urinary excretion is the primary route of elimination of azacitidine and/or its metabolites. Following intravenous and subcutaneous administration of ^{14}C-azacitidine, 50-85 % of the administered radioactivity was recovered in urine, while < 1 % was recovered in faeces.

Special populations

The effects of renal or hepatic impairment (see SPC section 4.2), gender, age, or race on the pharmacokinetics of azacitidine have not been formally studied.

Overall, the non-clinical and clinical studies have elucidated that the renal excretion of unchanged azacitidine is minor and that spontaneous hydrolysis products provides a major portion of urinary metabolites. Therefore, it is not anticipated that renal impairment will significantly alter the pharmacokinetics of parent azacitidine. However, as the kidney does play a significant role in the excretion of azacitidine and its metabolites, a study to assess the effects of renal impairment on the disposition of azacitidine in adult cancer patients will be submitted.

The effects of hepatic impairment on the pharmacokinetics of azacitidine have not been studied. Azacitidine appears not to be metabolised by hepatic CYPs, UGTs, SULTs or GSTs and the proposed SPC advises caution in patients with hepatic impairment.

Pharmacogenomics

The effect of known cytidine deaminase polymorphisms on azacitidine metabolism has not been formally investigated.

Plasma protein binding of azacitidine has not been directly evaluated.

Azacitidine can reactivate latent viruses such as Epstein Barr Virus (EBV) *in vitro* (tissue culture) and can induce EBV antigen production in EBV+ patients treated with azacitidine. However, no link between re-activation of latent viruses leading to overt clinical disease in patients treated with azacitidine has been found.

No formal clinical drug interaction studies with azacitidine have been conducted.

The applicant committed to submit the results of a Phase I, Open-Label, Dose-Escalation Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Oral Azacitidine in Subjects With Myelodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia, as a follow-up measure.

Clinical efficacy

The efficacy of azacitidine in the treatment of MDS was based on 4 studies (table 11): the pivotal study AZA-001, the Phase III supportive study CALGB 9221 and 2 additional Phase II uncontrolled studies CALGB 8921 and CALGB 8421.

Table 11 Overview of azacitidine studies to support efficacy in MDS patients

	AZA-001 Phase 3 Study (N=358)	Subcutaneous CALGB 9221 Phase 3 Study (N=191)	CALGB 8921 Phase 2 Study (N=72)	Intravenous CALGB 8421 Phase 2 Study (N=49)
No. of MDS patient treated with azacitidine	175	99	70	48
Patient population	RAEB, RAEB-T or CMMoL w/ IPSS High or INT-2	RA, RARS, RAEB, RAEB-T or CMMoL	RAEB, RAEB-T or CMMoL	RAEB, RAEB-T
Type of control	Controlled	Controlled	Uncontrolled	Uncontrolled
Comparator arm	CCR	BSC	N/A	N/A
Study sponsorship	Applicant	CALGB/NCI	CALGB/NCI	CALGB/NCI
Dose regimen	75 mg/m^2 s.c. x 7d q 28d	75 mg/m^2 s.c. x 7d q 28d	75 mg/m^2 s.c. x 7d q 28d	75 mg/m^2 i.v. x 7d q 28d
Primary purpose of study	Pivotal efficacy	Supportive efficacy	Supportive efficacy	Supportive efficacy (Pilot study)
Primary endpoint	Overall Survival	Response rate	Response rate	Response rate

- Dose response study (ies)

The proposed dosage regimen of azacitidine is based on clinical results obtained in the supportive studies CALGB 8421 and CALGB 8921. It was demonstrated that azacitidine is active in the treatment of higher-risk MDS when given i.v. or s.c. at 75 mg/m^2/day for 7 consecutive days every 28 days. This dosage was initially based on the clinical experience earlier obtained with azacitidine at 140 mg/day, for the treatment of sickle cell anaemia and beta thalassemia.

Study AZA-001 and the Phase III study CALGB 9221 were initiated with the same starting dose for azacitidine (75 mg/m^2/day, subcutaneously, for 7 days, q4w) and activity was observed with an acceptable toxicity profile.

In study AZA-001, bone marrow samples for methylation testing were collected for assessing the relationship between the effect of azacitidine with DNA demethylation and clinical response and/or adverse events. However, no proper dose response has been formally established. The effects of dose-response or exposure-response data of azacitidine on DNA demethylation effects and data on the relationship between a level of DNA demethylation and response rate and/or adverse events were not investigated in these trials.

- Main study (ies)

Study AZA-001 entitled "A Multicenter, Randomized, Open-Label, Parallel-Group, Phase 3 Trial of Subcutaneous Azacitidine Plus Best Supportive Care Versus Conventional Care Regimens Plus Best Supportive Care for the Treatment of Myelodysplastic Syndromes (MDS)" is the main pivotal study submitted by the applicant to support the claimed indication for azacitidine.

METHODS

Study participants

The study was a controlled, randomized, open label, parallel-group design Phase III study conducted in 79 sites from 15 countries.

The main eligibility criteria were:

- Patients ≥ 18 years with a life expectancy ≥ 3 months
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- an IPSS classification of Intermediate-2 (INT-2) or high; primary MDS diagnosed as RAEB or RAEB-T (FAB classification) or CMMoL (modified FAB classification) with monocytosis in peripheral blood > 1 x 10^9/l, dysplasia in 1 or more myeloid cell lines, 10 to 29% blasts in the bone marrow, and white blood cells < 13,000 x 10^6/l
- no prior treatment with transplantation or cytotoxic therapy

- unlikely to proceed to bone marrow or stem cell transplantation following remission.

Treatments

Patients were randomised in 1:1 ratio between the following 2 treatment groups:

- azacitidine 75 mg/m^2 s.c. for 7 days every 28 days plus best supportive care (BSC) or
- conventional care treatment regimen (CCR) plus BSC.

The conventional care treatment regimen consisted of 3 options (one of which was to be determined for all patients by the investigator prior to randomisation to avoid potential bias):

- BSC only
- BSC in addition to low-dose cytarabine SC for 20 mg/m^2/day for 14 days every 28 to 42 days until the end of the study or
- BSC in addition to standard chemotherapy administered for induction, as a continuous intravenous infusion of cytarabine 100 to 200 mg/m^2/day IV for 7 days with an anthracycline (daunorubicin, idarubicin or mitoxantrone) on Day 1, 2 and 3 and for those eligible, 1 or 2 consolidation cycles administered as continuous intravenous infusions of cytarabine for 3 to 7 days with the same anthracycline that was used at induction on days 1 and 2 (each cycle between 28 to 70 days from the start of the previous cycle).

Eligible patients were randomized to 1 of the 2 treatment groups with stratification by FAB and IPSS classification (RAEB/INT-2, RAEB/high, RAEB-T/INT-2, or RAEB-T/high) (patients diagnosed with CMMoL were to be randomized to the FAB stratum of RAEB or RAEB-T based on their bone marrow blast counts: those with counts 10% to 20% as RAEB, those with 21% to 29% as RAEB-T).

Treatment options in the conventional care regimens were assigned by the investigator based on local practice and on evaluation of the patient's underlying disease condition at the time of screening. Treatment assignment was not changed after randomisation.

Objectives

Primary study objective was to determine the effect of azacitidine plus BSC as compared with CCR plus BSC on overall survival in MDS patients.

Secondary objectives were to determine the effect of azacitidine plus BSC, relative to that of CCR plus BSC, on:

- time to AML transformation or death from any cause.
- time-to-transformation to AML defined as the number of days from the date of randomisation until the date of documented AML transformation, defined as a bone marrow blast count ≥ 30% independent of baseline bone marrow count and censored at death
- haematologic status (peripheral counts, need for platelet and red blood cell transfusions and status according to IWG criteria [haematologic response and haematologic improvement]) and episodes of infections requiring IV antibiotics (antibacterial or antifungal) or antivirals
- time-to-relapse after complete remission (CR) or partial remission (PR) or disease progression (according to IWG criteria), censored at death
- safety and toxicity azacitidine plus BSC, relative to that of CCR plus BSC, in MDS patients
- to examine the pharmacoeconomic differences in MDS patients treated with azacitidine plus BSC, as compared with patients receiving CCR plus BSC (data not shown).

Outcomes/endpoints

The primary efficacy endpoint was overall survival as defined as defined as the number of days from the date of randomisation until the date of death from any cause.

The secondary endpoints were time to transformation to AML (bone marrow blast > 30%) or death, time to transformation to AML, haematologic response (and improvements) and cytogenetic response based on 2000 IWG criteria for MDS, time to disease progression, relapse after CR or PR or death, transfusion status and number of on-treatment AE of severe infection.

Sample size

The protocol specified that 354 patients were to be randomised over an estimated period of 18-months and monitored for at least 12 months of treatment and follow-up. This would result in about 167 deaths after study duration of 30 months. A log rank analysis of 167 deaths would have approximately 90% power to detect a difference in overall survival curves characterised by a hazard ratio of 0.60 (median overall survival of 18.3 months for azacitidine and 11 months for CCR).

Randomisation

This study used blocked randomisation that stratified patients by FAB and IPSS classifications to ensure a balanced assignment of patients to the 2 treatment groups. This randomisation process used a remote centralised system.

Blinding (masking)

The study is an open-label study, but the haematological response (and its duration) for the primary analysis (though not haematological improvement), the FAB and WHO diagnoses, IPSS classifications and IWG was performed by a blinded independent central reviewer.

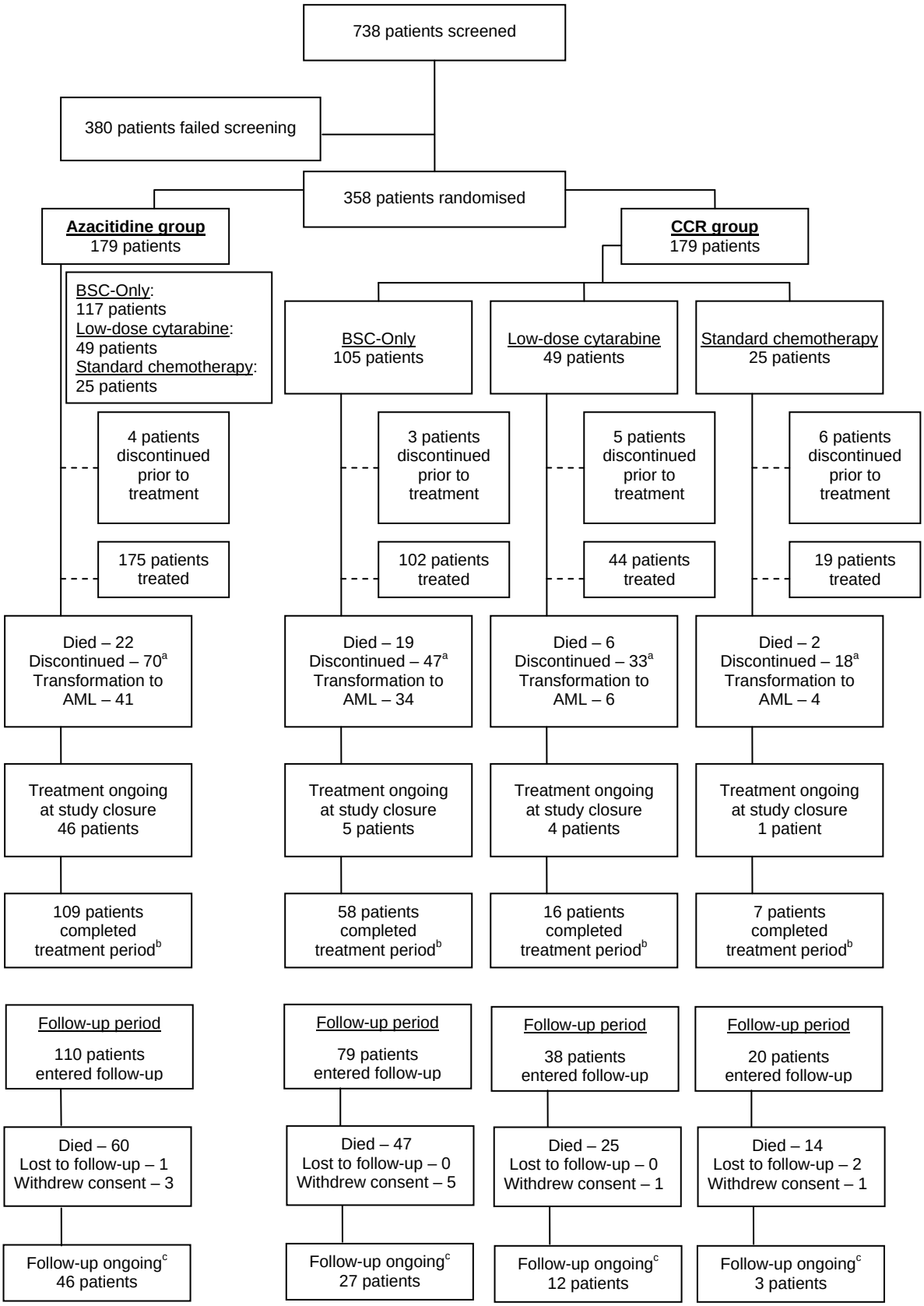
Statistical methods

For purposes of time-to-event analyses involving death and transformation to AML, the duration was defined as the time from the date of randomisation to the minimum of the date of death or the date of censor. The date of censor could be due to administrative censoring (for interim or final analysis), date of last contact if the patient was lost to follow-up or date the patient withdrew consent from follow-up. For the analyses during the treatment period, the censor date could have been the patient's last treatment study visit (if this was the minimum date among date of death, AML or last contact).

RESULTS

Participant flow

Figure 3 Study AZ-001 – Patient disposition



a 1 patient in the azacitidine group, 2 in the BSC-only group, 1 in the low-dose cytarabine group, and 2 in the standard chemo group withdrew consent for follow-up and did not enter the follow-up period.

b Patients who completed the treatment period included those who died or transformed to AML during the treatment period, or were receiving study drug at the time of study closure.

c Patients were still in follow-up at the time of study closure. Follow-up was terminated at the time of the final study close-out visit.

Recruitment

The trial enrolled 738 patients and randomised 358 over 30 months and the study duration lasted 44 months. This resulted in 195 deaths (16.8% more deaths than originally planned) and 95% power for this trial under the design assumptions of the protocol.

Conduct of the study

Overall, 30.2% of patients treated with azacitidine and 39.1% treated with CCR had at least 1 major protocol deviation. The most frequently observed protocol deviations are presented in table 12.

Table 12 Study AZA-001 - Major protocol deviations

	Azacitidine	**Conventional care regimens**			
		BSC only	**Low-dose cytarabine**	**Standard chemotherapy**	**Combined CCR**
	N=179	**N=105**	**N=49**	**N=25**	**N=179**
Patients with at least 1 major protocol deviation	54 (30.2)	33 (31.4)	24 (49.0)	13 (52.0)	70 (39.1)
Patient took prohibited medication at any time during the treatment period[a]	19 (10.6)	6 (5.7)	2 (4.1)	3 (12.0)	11 (6.1)
Did not receive a minimum number of treatment cycles[b]	16 (8.9)	9 (8.6)	13 (26.5)	6 (24.0)	28 (15.6)
Patient crossed over to any active therapy for MDS	10 (5.6)	12 (11.4)	7 (14.3)	1 (4.0)	20 (11.2)

a Prohibited medication included interleukin-11, thalidomide, arsenic trioxide, interferon, retinoids (e.g., all-trans retinoic acids), erythropoietin, corticosteroids at doses > 100 mg hydrocortisone, use of G-CSF/GM-CSF for a reason other than a concurrent infection.

b Minimum number of cycles=1 cycle for standard chemotherapy, 2 cycles for azacitidine and low-dose cytarabine, did not remain in the treatment period for at least 28 days for BSC only.

Baseline data

Baseline patient demographics for the ITT population are summarised overall and per treatment group in tables 13 and 14 and disease characteristics in table 15.

Table 13 Study AZA-001 - Baseline demographic characteristics (ITT)

	Azacitidine	Conventional care regimen				Total
		BSC only	Low-dose cytarabine	Standard chemotherapy	Combined CCR	
	N=179	N=105	N=49	N=25	N=179	N=358
Gender						
Male	132 (73.7)	67 (63.8)	35 (71.4)	17 (68.0)	119 (66.5)	251 (70.1)
Female	47 (26.3)	38 (36.2)	14 (28.6)	8 (32.0)	60 (33.5)	107 (29.9)
Race						
Caucasian	177 (98.9)	104 (99.0)	47 (95.9)	24 (96.0)	175 (97.8)	352 (98.3)
Black or African American	0	0	0	0	0	0
Asian/Oriental	2 (1.1)	1 (1.0)	2 (4.1)	0	3 (1.7)	5 (1.4)
Hispanic	0	0	0	1 (4.0)	1 (0.6)	1 (0.3)
Other	0	0	0	0	0	0
Age (years)						
Mean ± Std Dev	68.0 ± 7.57	69.9 ± 7.68	70.6 ± 6.93	63.4 ± 8.18	69.2 ± 7.87	68.6 ± 7.73
Median	69.0	70.0	71.0	65.0	70.0	69.0
Min, Max	42, 83	50, 88	56, 85	38, 76	38, 88	38, 88
Age categories						
≤ 44	1 (0.6)	0	0	1 (4.0)	1 (0.6)	2 (0.6)
45-54	5 (2.8)	2 (1.9)	0	2 (8.0)	4 (2.2)	9 (2.5)
55-64	51 (28.5)	22 (21.0)	7 (14.3)	9 (36.0)	38 (21.2)	89 (24.9)
65-74	84 (46.9)	48 (45.7)	28 (57.1)	11 (44.0)	87 (48.6)	171 (47.8)
≥ 75	38 (21.2)	33 (31.4)	14 (28.6)	2 (8.0)	49 (27.4)	87 (24.3)
Weight (kg)						
Mean ± Std Dev	76.5 ± 14.08	74.9 ± 14.30	74.2 ± 12.17	73.9 ± 13.43	74.6 ± 13.58	75.6 ± 13.85
Median	75.1	76.0	75.0	74.5	75.2	75.2
Min, Max	47, 134	43, 113	50, 118	39, 93	39, 118	39, 134
BSA (m^2)						
Mean ± Std Dev	1.9 ± 0.19	1.8 ± 0.20	1.8 ± 0.17	1.8 ± 0.20	1.8 ± 0.19	1.9 ± 0.19
Median	1.9	1.8	1.9	1.9	1.9	1.9
Min, Max	1.4, 2.5	1.3, 2.2	1.4, 2.3	1.2, 2.0	1.2, 2.3	1.2, 2.5

Table 14 Study AZA-001 - Baseline IPSS as assessed by IRC (ITT)

	Azacitidine	Conventional care regimen				Total
		BSC only	Low-dose cytarabine	Standard chemotherapy	Combined CCR	
	N=179	N=105	N=49	N=25	N=179	N=358
IPSS[a]						
INT-1 (0.5 to 1.0)	5 (2.8)	9 (8.6)	2 (4.1)	2 (8.0)	13 (7.3)	18 (5.0)
INT-2 (1.5 to 2.0)	76 (42.5)	46 (43.8)	21 (42.9)	3 (12.0)	70 (39.1)	146 (40.8)
High (≥ 2.5)	82 (45.8)	46 (43.8)	21 (42.9)	18 (72.0)	85 (47.5)	167 (46.6)
Not applicable	5 (2.8)	0	1 (2.0)	2 (8.0)	3 (1.7)	8 (2.2)
Indeterminate	11 (6.1)	4 (3.8)	4 (8.2)	0	8 (4.5)	19 (5.3)
BM blasts						
≥ 5 to ≤ 10	28 (15.6)	22 (21.0)	7 (14.3)	3 (12.0)	32 (17.9)	60 (16.8)
> 10 to ≤ 20	99 (55.3)	59 (56.2)	21 (42.9)	11 (44.0)	91 (50.8)	190 (53.1)
> 20 to ≤ 30	50 (27.9)	23 (21.9)	17 (34.7)	10 (40.0)	50 (27.9)	100 (27.9)
> 30	1 (0.6)	0	0	1 (4.0)	1 (0.6)	2 (0.6)
Missing	1 (0.6)	1 (1.0)	4 (8.2)	0	5 (2.8)	6 (1.7)
Cytogenetics						
Good	83 (46.4)	47 (44.8)	28 (57.1)	9 (36.0)	84 (46.9)	167 (46.6)
Intermediate	37 (20.7)	23 (21.9)	12 (24.5)	4 (16.0)	39 (21.8)	76 (21.2)
Poor	50 (27.9)	31 (29.5)	8 (16.3)	11 (44.0)	50 (27.9)	100 (27.9)
Missing	9 (5.0)	4 (3.8)	1 (2.0)	1 (4.0)	6 (3.4)	15 (4.2)
Cytopenias[b]						
1	11 (6.1)	10 (9.5)	4 (8.2)	0	14 (7.8)	25 (7.0)
2	62 (34.6)	42 (40.0)	20 (40.8)	13 (52.0)	75 (41.9)	137 (38.3)
3	106 (59.2)	52 (49.5)	24 (49.0)	12 (48.0)	88 (49.2)	194 (54.2)
Missing	0	1 (1.0)	1 (2.0)	0	2 (1.1)	2 (0.6)
Haemoglobin						
< 80 g/l	15 (8.4)	18 (17.1)	3 (6.1)	3 (12.0)	24 (13.4)	39 (10.9)
≥ 80 g/l	128 (71.5)	62 (59.0)	29 (59.2)	19 (76.0)	110 (61.5)	238 (66.5)
Missing	36 (20.1)	25 (23.8)	17 (34.7)	3 (12.0)	45 (25.1)	81 (22.6)
Platelets						
< 20 x 10^9/l	22 (12.3)	15 (14.3)	2 (4.1)	3 (12.0)	20 (11.2)	42 (11.7)
≥ 20 x 10^9/l	142 (79.3)	81 (77.1)	43 (87.8)	20 (80.0)	144 (80.4)	286 (79.9)
Missing	15 (8.4)	9 (8.6)	4 (8.2)	2 (8.0)	15 (8.4)	30 (8.4)
ANC						
< 0.5 x 10^9/l	39 (21.8)	29 (27.6)	7 (14.3)	7 (28.0)	43 (24.0)	82 (22.9)
≥ 0.5 x 10^9/l	129 (72.1)	73 (69.5)	38 (77.6)	16 (64.0)	127 (70.9)	256 (71.5)
Missing	11 (6.1)	3 (2.9)	4 (8.2)	2 (8.0)	9 (5.0)	20 (5.6)

a This score was determined by the Independent Review Committee

b There are 6 and 23 patients with partial cytopenia data grouped with 1 and 2 cytopenias, respectively

Note Baseline bone marrow blasts are the average of all relative bone marrow blast values collected for the 56 days prior to and including the date of randomisation. Percentages are based on the number of patients in each treatment group.

Table 15 Study AZA-001 - Baseline disease characteristics regarding PS, time of diagnosis and transfusions needed (ITT)

	Azacitidine	Conventional care regimen				Total
		BSC only	Low-dose cytarabine	Standard chemotherapy	Combined CCR	
	N=179	N=105	N=49	N=25	N=179	N=358
ECOG performance status						
0	78 (43.6)	36 (34.3)	29 (59.2)	15 (60.0)	80 (44.7)	158 (44.1)
1	86 (48.0)	59 (56.2)	17 (34.7)	10 (40.0)	86 (48.0)	172 (48.0)
2	13 (7.3)	8 (7.6)	2 (4.1)	0	10 (5.6)	23 (6.4)
Missing	2 (1.1)	2 (1.9)	1 (2.0)	0	3 (1.7)	5 (1.4)
Time since original diagnosis (years)						
Mean ± Std deviation	1.2 ± 1.91	1.2 ± 1.90	1.2 ± 2.44	1.2 ± 2.55	1.2 ± 2.15	1.2 ± 2.03
Min, Max	0, 10	0, 10	0, 11	0, 12	0, 12	0, 12
< 1 year	92 (51.4)	53 (50.5)	28 (57.1)	14 (56.0)	95 (53.1)	187 (52.2)
1 to < 2 years	37 (20.7)	27 (25.7)	12 (24.5)	6 (24.0)	45 (25.1)	82 (22.9)
2 to < 3 years	20 (11.2)	6 (5.7)	3 (6.1)	1 (4.0)	10 (5.6)	30 (8.4)
≥ 3 years	30 (16.8)	19 (18.1)	6 (12.2)	4 (16.0)	29 (16.2)	59 (16.5)
Transfusion product used in 56 days before randomisation						
Any transfusion product	115 (64.2)	72 (65.6)	33 (67.3)	12 (48.0)	117 (65.4)	232 (64.8)
Blood cells, packed human	111 (62.0)	72 (68.7)	30 (61.2)	12 (48.0)	114 (63.7)	225 (62.8)
Platelets	38 (21.2)	13 (12.4)	12 (24.5)	2 (8.0)	27 (15.1)	65 (18.2)
Number of RBC transfusions						
Mean ± Std deviation	1.9 ± 2.22	2.0 ± 2.10	2.0 ± 2.51	1.0 ± 1.31	1.9 ± 2.15	1.9 ± 2.18
Median	1.0	2.0	1.0	0	1.0	1.0
Min, Max	0, 10	0, 9	0, 10	0, 4	0, 10	0, 10
Number of platelet transfusions						
Mean ± Std deviation	0.7 ± 1.85	0.5 ± 1.61	0.8 ± 2.29	0.2 ± 0.82	0.5 ± 1.75	0.6 ± 1.80
Median	0	0	0	0	0	0
Min, Max	0, 14	0, 10	0, 14	0, 4	0, 14	0, 14

a Time since original diagnosis to date of informed consent

Numbers analysed

Disposition of patients included in study AZA-001 is shown in figure 3, 179 patients were randomised to the azacitidine treatment group and 179 to the combined CCR treatment group; these patients comprised the ITT population.

The PP population consisted of 234 (65.4%) patients, 54 patients in the azacitidine-treatment group and 70 in the CCR group eventually encountered ≥ 1 major protocol violation and were excluded from the per protocol population (table 12).

The safety population is comprised of 340 (95.0%) patients who received at least 1 dose of study drug and had at least one post-dose safety assessment. Because BSC-only treatment may consist of blood products or antibiotics administered only as needed, patients randomised to the CCR group and assigned to BSC-only were included in the safety population if they had at least 1 post-randomisation assessment.

Outcomes and estimation

The primary efficacy endpoint, an analysis of OS (time-to-death from any cause) for the ITT population by treatment group as defined by the number of days from randomization date until death by any cause, is provided in table 16. A Kaplan Meier plot of time to death from any cause by treatment group for the ITT population is presented in figure 4.

Table 16 Study AZA-001 - Summary of time-to-death from any cause (ITT)

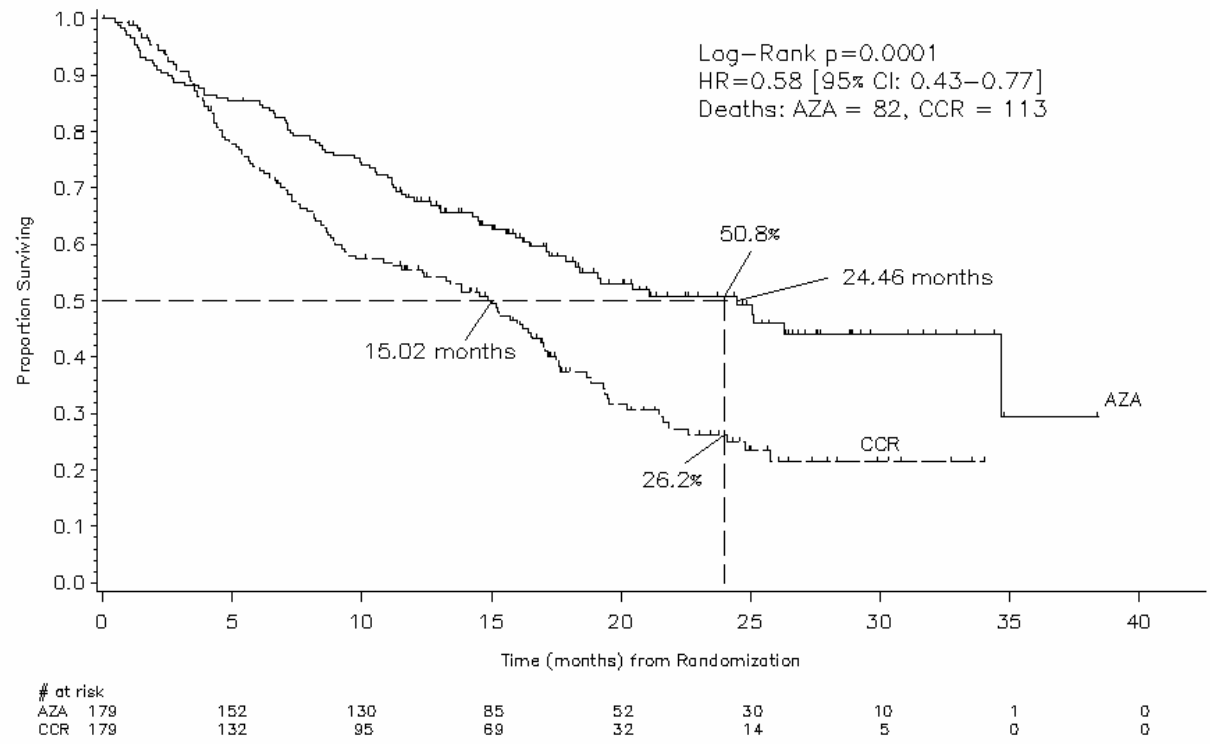
	Azacitidine N=179	Combined CCR N=179	Difference
Deaths - n (%)	82 (45.8)	113 (63.1)	
Overall Survival time (months)			
Kaplan-Meier median	24.46	15.02	9.44
95% CI on median	17.9, DNE	9.8, 17.0	
Log-rank p-value[a]		0.0001	
Hazard ratio (95% CI)[b]		0.58 (0.43, 0.77)	
p-value		0.0002	
Hazard ratio (95% CI)[c]		0.59 (0.44, 0.79)	
p-value		0.0004	

a The p value is two-sided from the log rank test stratified by the randomisation stratification factors of IPSS classification and FAB classification per central review which compares whether the azacitidine and combined CCR groups follow the same survival curve

b Cox proportional hazards model stratified on the randomisation factors of FAB and IPSS with model term of treatment

c Cox proportional hazards model stratified on the randomisation factors of FAB and IPSS with model terms of treatment, gender, age and investigator's selection of conventional care regimen

Figure 4 Study AZA-001 – Kaplan Meier plot of time to death any cause (ITT)



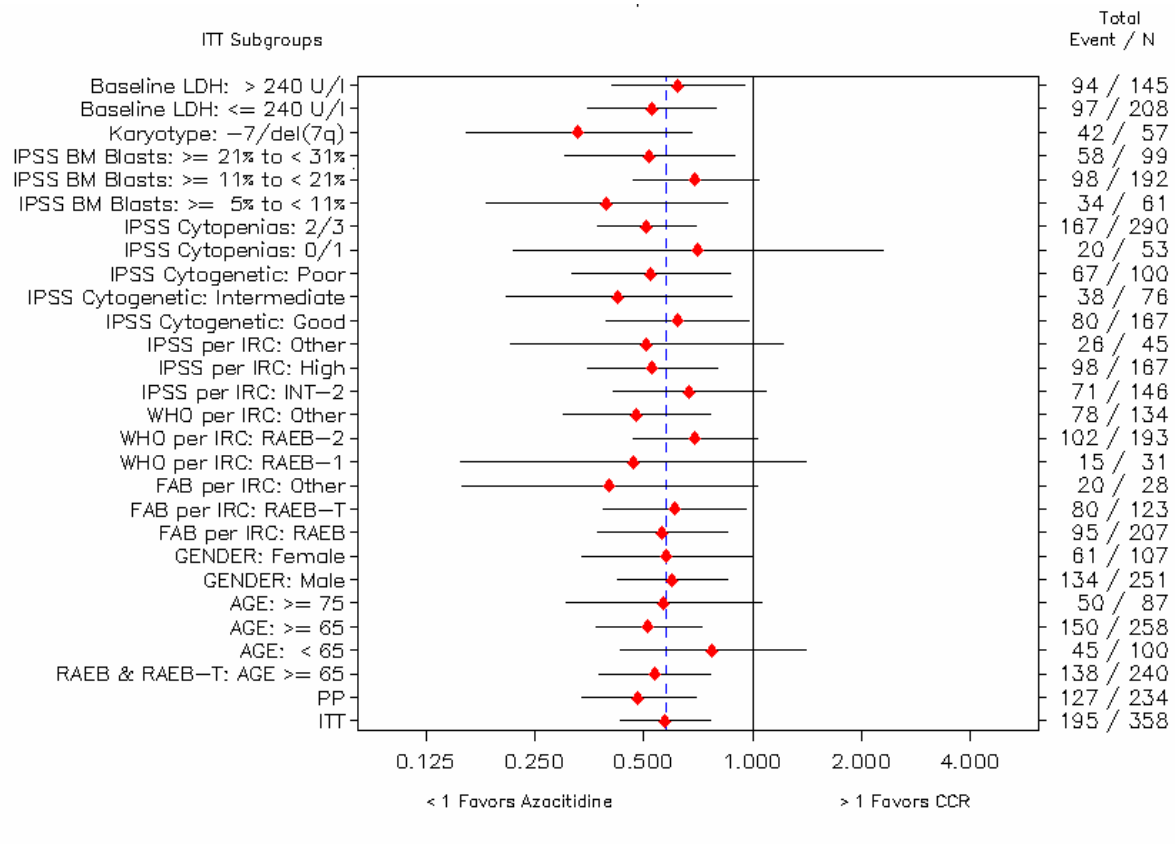
The Kaplan Meier median overall survival times were 24.5 months and 15.0 months in the azacitidine and combined CCR groups, respectively. Azacitidine was statistically superior to the combined CCR group for prolonging survival, with an increase in median survival of 9.4 months (stratified log rank p = 0.0001). The Kaplan Meier time to the first quartile was 10.5 and 5.1 months for azacitidine and combined CCR, respectively, for a difference of 4.8 months (95% CI 0.8, 8.7 months; p = 0.0178).

Subgroup analyses were performed. Each set of CCR subgroup patients have been compared with either a) all azacitidine recipients or b) the set of azacitidine recipients that would have received the same CCR treatment if they had been randomised to the control group. Similar to the ITT analysis, the Kaplan Meier median time-to-death was longer in each of the azacitidine groups (by approximately 9.5 months) compared with the CCR groups within each selection group and the risk of death in the azacitidine group was reduced compared with CCR. The difference in the survival curves was statistically different in the BSC selection group; they were not statistically different in the low-dose cytarabine and standard chemotherapy selection groups due to the low patient numbers.

An analysis in the PP population by treatment group provided similar survival advantage as observed in the ITT population (10.1 vs. 9.4 months, respectively).

Sensitivity analyses demonstrated no meaningful changes to the conclusions regarding the effect of azacitidine on overall survival.

Figure 5: Hazard ratio and 95% confidence interval for overall survival by subgroup for azacitidine versus combined CCR (ITT population)



The effect of treatment on the primary endpoint was performed for the pre-specified subgroups of age, gender, FAB classification, FAB classification and ≥ 65 years old, WHO classification, IPSS, IPSS cytogenetic risk group, IPSS cytopenia risk group, IPSS bone marrow blast risk group, -7/del(7q) karyotype and LDH and showed that the azacitidine group had a reduced risk of death compared with patients in the combined CCR group for all subgroups (the ITT hazard ratio [0.58] is included within the confidence interval of all subgroups) (see figure 5).

A summary of the secondary efficacy endpoints is provided in table 17.

Table 17 Study AZA-001 - Summary of secondary efficacy endpoints (ITT)

	Azacitidine N=179	Combined CCR N=179	Difference
Time-to-transformation to AML or death			
In percentage	120 (67.0)	132 (73.7)	
Kaplan-Meier median (months)	13.02	7.61	5.41
95% CI on median	9.9, 15.0	5.4, 9.8	
Log-rank p-value[a]		0.0025	
Hazard ratio (95% CI)[b]		0.68 (0.53, 0.87)	
p-value		0.0027	
Hazard ratio (95% CI)[c]		0.67 (0.52, 0.87)	
p-value		0.0022	
Time-to-transformation to AML			
In percentage	78 (43.6)	71 (39.7)	
Kaplan-Meier median (months)	20.66	15.44	5.21
95% CI on median	14.9, 25.5	12.4, 22.5	
Log-rank p-value[a]		0.2555	
Hazard ratio (95% CI)[b]		0.83 (0.60, 1.15)	
p-value		0.2562	
Hazard ratio (95% CI)[c]		0.80 (0.57, 1.11)	
p-value		0.1782	

a The p value is two-sided from the log rank test stratified by the randomisation stratification factors of IPSS classification and FAB classification per central review which compares whether the azacitidine and CCR group follow the same survival curve.

b Cox proportional hazards model stratified on the randomisation factors of FAB and IPSS with model term of treatment

c Cox proportional hazards model stratified on the randomisation factors of FAB and IPSS with model terms of treatment, gender, age, and investigator's selection of conventional care regimen

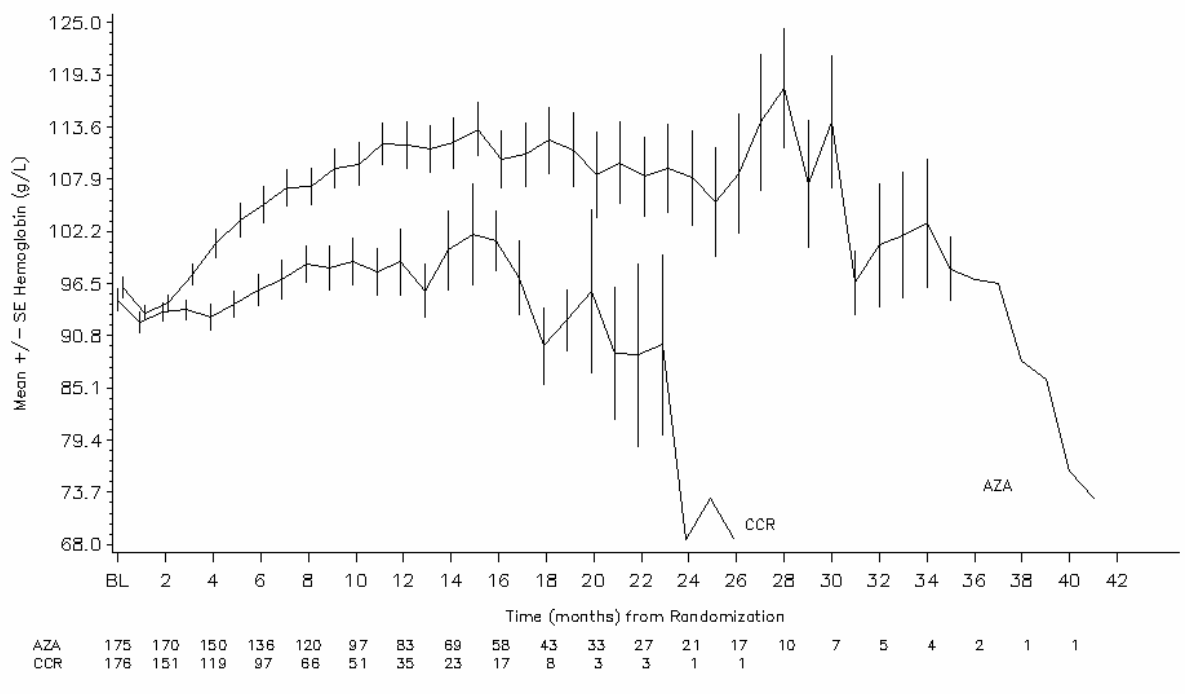
For the secondary efficacy endpoints, time to transformation to AML or death showed consistent results where a median of 13.02 months compared to 7.61 months was observed in the azacitidine and combined CCR group, respectively, a difference of 5.41 months. Similar results were obtained in time –to–transformation to AML only.

Sensitivity analyses demonstrated no meaningful changes to the conclusions regarding the effect of azacitidine on time –to–transformation to AML.

The mean haemoglobin concentration in the azacitidine and CCR groups is depicted in figure 6.

The total number of RBC transfusions was 1799 in the azacitidine group and 1754 in the CCR group. When taken into account the number of patient-years, the RBC transfusion rate favoured azacitidine group: 10.63 and 18.33 per patient-year for azacitidine- and the CCR group, respectively. Of the 111 patients in the azacitidine group who were RBC transfusion dependent at baseline, 45.0% of these patients became RBC transfusion independent during the treatment period, compared with 11.4% of the patients in the combined CCR group ($p < 0.0001$). The 33.6% difference (95% CI 22.4, 44.6) was statistically significant ($p<0.0001$).

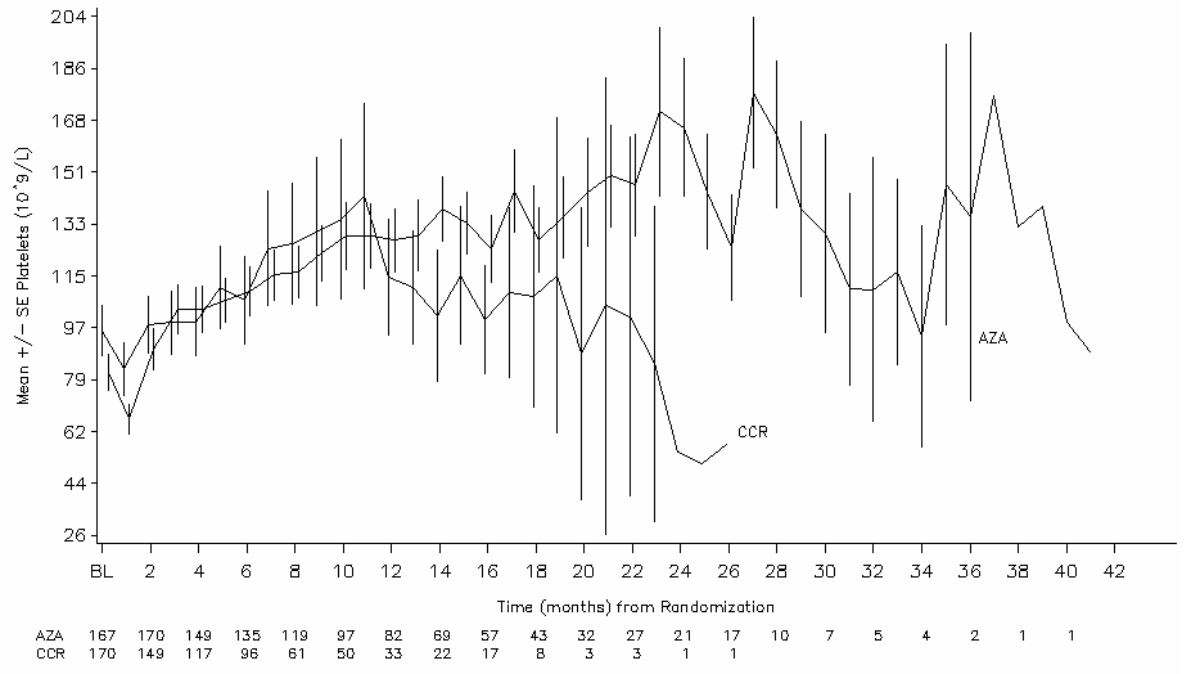
Figure 6 Study AZA-001 – Mean haemoglobin concentrations over time (ITT)



The number of platelet transfusions per patient-year was slightly higher in the combined CCR group (9.4) compared with the azacitidine group (6.0). The percentage of patients who were platelet transfusion dependent at baseline and became platelet transfusion independent during the treatment period was similar in the azacitidine (42.1%) and CCR group (40.7%) but remained longer platelet transfusion independent (approximately 7 months) in the azacitidine group. In patients who were platelet transfusion independent at baseline, 89.4% of the azacitidine patients remained platelet transfusion independent during the treatment period, compared with 67.1% of the patients in the combined CCR group ($p < 0.0001$).

Figure 7 provides a plot of mean platelet counts over time in the azacitidine and combined CCR groups.

Figure 7 Study AZA-001 – Mean platelet counts over time (ITT)



Response assessment encompassed Overall Response Rate (ORR), i.e., CR+PR+SD, Response Rate (CR +PR), haematologic improvement (laboratory responses, i.e., haemoglobin, neutrophil count, platelet count) and cytogenetic response based on International Working Group (IWG) criteria for MDS (65), were assessed by the investigator as well as by IRC (table 18).

Table 18 Study AZA-001 - Summary of response assessment using the IWG (2000) criteria (ITT)

	Number (%) of Patients				p-value[a]
	Azacitidine N=179		Combined CCR N=179		
Investigator determined response					
Overall Response Rate (ORR)	179	126 (70.4)	179	86 (48.0)	< 0.0001
Response Rate	179	51 (28.5)	179	21 (11.7)	0.0001
Complete Remission (CR)	179	30 (16.8)	179	14 (7.8)	0.0150
Partial Remission (PR)	179	21 (11.7)	179	7 (3.9)	0.0094
Stable Disease (SD)	179	75 (41.9)	179	65 (36.3)	0.3297
Relapse after CR or PR	51	10 (19.6)	21	4 (19.0)	1.0000
Disease Progression	179	48 (26.8)	179	26 (14.5)	0.0059
Transformation to AML	179	53 (29.6)	179	53 (29.6)	1.0000
IRC determined response					
Overall Response Rate (ORR)	179	**163 (91.1)**	179	**140 (78.2)**	0.0011
Response Rate	179	**12 (6.7)**	179	**2 (1.1)**	0.0113
Complete Remission (CR)	179	**7 (3.9)**	179	**2 (1.1)**	0.1741
Partial Remission (PR)	172	**5 (2.9)**	179	**0**	0.0282
Stable Disease (SD)	179	**151 (84.4)**	179	**138 (77.1)**	0.1074
Relapse after CR or PR	12	11 (91.7)	2	2 (100.0)	1.0000
Disease Progression	179	64 (35.8)	179	54 (30.2)	0.3116
Transformation to AML	179	52 (29.1)	179	45 (25.1)	0.4757
Haematologic improvement (HI) [b]					
Any improvement	177	**87 (49.2)**	178	**51 (28.7)**	< 0.0001
Erythroid Response					
Major	157	62 (39.5)	160	17 (10.6)	< 0.0001
Minor	157	2 (1.3)	160	1 (0.6)	0.6203
Platelet Response					
Major	141	46 (32.6)	129	18 (14.0)	0.0003
Minor	138	6 (4.3)	127	4 (3.1)	0.7514
Neutrophil Response					
Major	131	25 (19.1)	111	20 (18.0)	0.8695
Minor	131	5 (3.8)	111	9 (8.1)	0.1760
Progression/relapse after HI	87	47 (54.0)	51	27 (52.9)	1.0000
Cytogenetic response[b]					
Major	65	3 (4.6)	67	3 (4.5)	1.0000
Minor	65	22 (33.8)	67	7 (10.4)	0.0015

a The p value is from Fisher's exact test comparing the response rates between the azacitidine and the combined CCR groups

b Haematologic improvement and cytogenetic response were determined by the IRC

As determined by the IRC, the overall response rate (CR + PR + SD) was 91% in the azacitidine group compared with 78% in the combined CCR group; a statistically significant difference (p =0.0011). The median time to disease progression, relapse after CR or PR, or death from any cause was longer in the azacitidine group (14.1 months) compared with the combined CCR group (8.8 months), with a median increase of 5.3 months with azacitidine treatment (log rank p = 0.0466) investigators assessment. The percentage of patients in the azacitidine group (49%) with any haematologic improvement was 1.5-fold higher compared with the combined CCR group (29%).

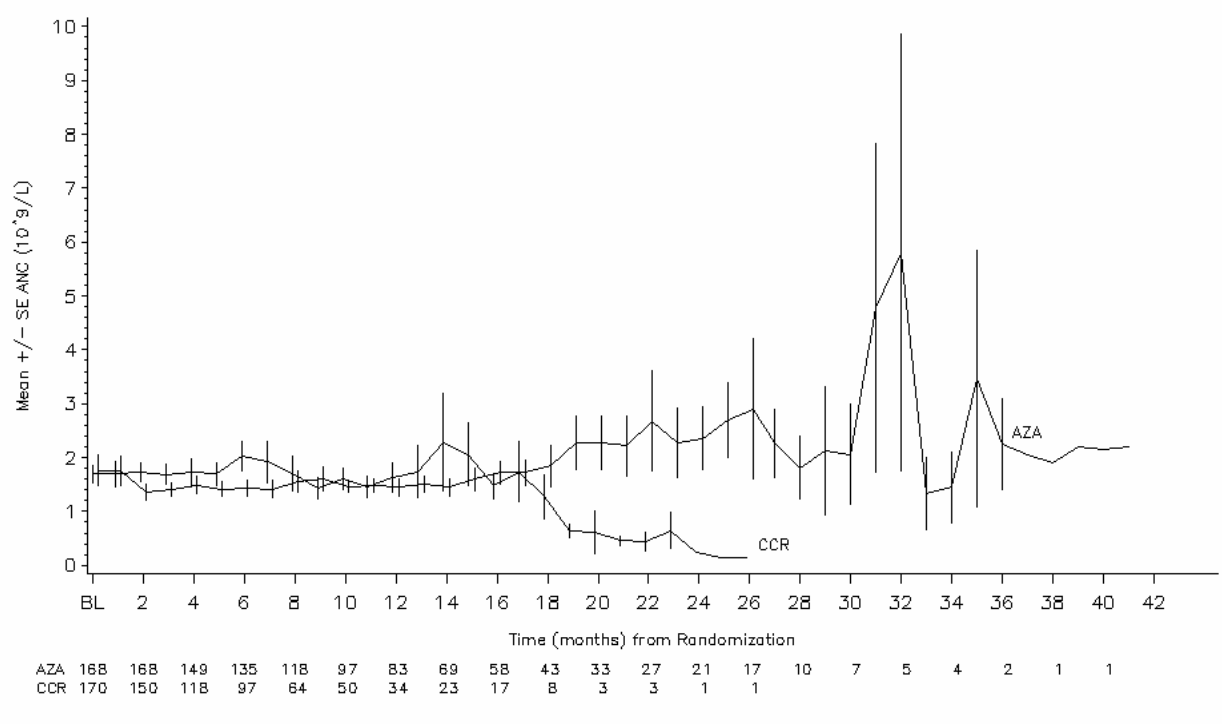
The percentage of patients in the azacitidine group (40%) with a major erythroid response was 3.5-fold higher compared with the combined CCR group (11%). Similarly, the percentage of patients in the azacitidine group (33%) with a major platelet response was 2-fold higher compared with the combined CCR group (14%). The median duration of haematologic improvement was longer in the azacitidine

group (13.6 months) compared with the CCR group (5.2 months) (log rank p = 0.0002). The hazard ratios of recurrent neutropenia and thrombocytopenia were 1.16 and 0.95 when azacitidine group was compared to the CCR group. The risk of recurrent anaemia was reduced by 11% in the azacitidine group compared with the combined CCR group (HR 0.89, p=0.0094).

Figure 8 provides a plot of mean absolute neutrophil counts over time in the azacitidine and combined CCR groups.

The percentage of patients with a major neutrophil response was similar in the azacitidine (19%) and combined CCR (18%) groups. The mean WBC curves for the azacitidine and combined CCR groups were generally similar until approximately 17 months, when the number of patients in the CCR group became small. The azacitidine group generally remained constant until the 30th month, when the number of patients became small.

Figure 8 Study AZA-001 – Mean absolute neutrophil counts over time (ITT)



The rate of infection requiring i.v. antibiotic, antifungal or antiviral therapy was 1.5-fold higher in the combined CCR group compared with the azacitidine group. There were 27 adverse events of infection that required therapy during 169 patient-years for a rate of 0.16 events per patient-year in the azacitidine group compared with 23 adverse events of infection during 96 patient-years at a rate of 0.24 events per patient-year in the CCR group. The relative risk of such infections was 0.67 (95% CI 0.35, 1.20; p = 0.1327) indicating 33% less risk of such infections for the azacitidine group relative to the CCR group. The risk of recurrent of infection requiring IV treatment was reduced by 11 and 21% in the azacitidine group and with the CCR-group, respectively. The reduced risk of infection was not statistically significantly different between the two groups.

- Supportive study (ies)

Supportive studies comprise one open-label, controlled, Phase III study (study CALGB 9221) and 2 open-label, uncontrolled, Phase II studies (studies CALGB 8421 and CALGB 8921). In these studies the primary endpoint was defined as the overall response rate (CR + PR).

Study CALGB 8421 initially planned for enrolment of up to 20 patients; however, based on the results of the first 13 patients, the enrolment goal was extended to 45 patients. Eventually 48 patients were enrolled to receive azacitidine 75 mg/m^2 as a continuous IV infusion for 7 days on a 28-day cycle for a minimum of 4 cycles.

Study CALGB 8921 initially planned for enrolment of up to 50 patients over the period of 1.5 years; patients were to receive 75 mg/m^2 azacitidine SC daily for 7 days on a 28-day cycle for a minimum of 4 cycles. A total of 72 patients were included as ITT population. The mean and median total duration of clinical response of PR or better for the responders was 565 days (1.5 years) and 117 days, respectively. The median survival times of the responders and of the non-responders were 39.3 and 9.6 months, respectively. The median times-to-transformation to AML of the responders (excluding AML patients) and the non-responders were 59.1 and 21.8 months, respectively. Other than Month 12, responders were transfusion-free from the 10th to month 18. Haemoglobin concentrations increased after the 2nd for all patients.

Study CALGB 9221 was an open-label, multicentre, controlled, Phase III trial, initiated in 1994, designed to compare azacitidine plus supportive care with an observation group receiving best supportive care only in patients with any of the 5 subtypes of MDS per the FAB classification (RA, RARS, RAEB, RAEB-T, or CMMoL). The use of a BSC-only group as a control was chosen because at the time the study was conducted, there was no approved treatment for MDS. A total of 191 patients (99 azacitidine, all of which received study medication, 92 observation) were enrolled and randomised in the study at 53 centres. Patients in the azacitidine treatment arm were to receive a starting dose of 75 mg/m^2 azacitidine SC daily for 7 days on a 28-day cycle for a minimum of 4 cycles.

The primary endpoint, overall response rate, in azacitidine group was 16.2% compared to 0% in the observation group. The mean time to transformation to AML in the azacitidine group was 45.8 months, compared with 23.5 months for the observation group (p=0.16). Median survival time, which was confounded by the cross-over design of this study, for the azacitidine group and observation group were respectively 20.1 months and 15.4 months (statistically not significant).

A summary of the results of CALGB studies is displayed in table 19.

Table 19 CALGB studies - Summary of response assessment (ITT)

	Subcutaneous			Intravenous
	CALGB 9221[a]		CALGB 8921[b]	CALGB 8421[c]
	Azacitidine N=99	BSC N=92	Azacitidine N=72	Azacitidine N=48
Response assessment				
Overall (CR + PR)	16 (16.2)	0 (0.0)	10 (13.9)	9 (18.8)
Complete Remission (CR)	6 (6.1)	0 (0.0)	4 (5.6)	3 (6.3)
Partial Remission (PR)	10 (10.1)	0 (0.0)	6 (8.3)	6 (12.5)
Time to death from any cause				
In percentage	95 (96.0)	86 (93.5)	70 (97.2)	
Median (months)	20.1	15.4	11.6	
95% CI on median	16.9, 26.4	13.4, 20.1	8.7, 17.8	
Log-rank p-value	0.6064		NA	
Time to transformation to AML or death (excluding patients with AML at baseline)				
In percentage	85 (95.5)	77 (92.8)	54 (98.2)	
Median (months)	17.7	13.8	10.1	
95% CI on median	14.2, 22.9	9.3, 16.4	5.9, 15.7	
Log-rank p-value	0.4789		NA	
Time to transformation to AML (excluding patients with AML at baseline)				
In percentage	31 (34.8)	33 (39.8)	22 (40.0)	
Median (months)	45.8	23.5	28.4	
95% CI on median	28.3, DNE	16.4, DNE	16.7, 117.2	
Log-rank p-value	0.1555		NA	

a Includes all 5 MDS subtypes RA, RARS, RAEB, RAEB-T, and CMMoL
b Includes all the MDS subtypes of RAEB, RAEB-T, and CMMoL
c Includes all the MDS subtypes of RAEB and RAEB-T

- Discussion on clinical efficacy

The clinical efficacy and safety of Vidaza were studied in an international, multicenter, controlled, open-label, randomised, parallel-group, Phase 3 comparative study (AZA PH GL 2003 CL 001) in patients with: intermediate-2 and high-risk MDS according to the International Prognostic Scoring

System (IPSS), refractory anaemia with excess blasts (RAEB), refractory anaemia with excess blasts in transformation (RAEB-T) and modified chronic myelomonocytic leukaemia (mCMML) according to the French American British (FAB) classification system. RAEB-T patients (21-30 % blasts) are now considered to be AML patients under the current WHO classification system. Azacitidine plus best supportive care (BSC) (n = 179) was compared to conventional care regimens (CCR). CCR consisted of BSC alone (n = 105), low-dose cytarabine plus BSC (n = 49) or standard induction chemotherapy plus BSC (n = 25). Patients were pre-selected by their physician to 1 of the 3 CCR prior to randomisation. Patients received this pre-selected regimen if not randomised to Vidaza. As part of the inclusion criteria, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients with secondary MDS were excluded from the study. The primary endpoint of the study was overall survival. Vidaza was administered at a subcutaneous (s.c.) dose of 75 mg/m^2 daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle) for a median of 9 cycles (range = 1-39) and a mean of 10.2 cycles. Within the Intent to Treat population (ITT), the median age was 69 years (range 38 to 88 years).

In the ITT analysis of 358 patients (179 azacitidine and 179 CCR), Vidaza treatment was associated with a median survival of 24.46 months *versus* 15.02 months for those receiving CCR treatment, a difference of 9.4 months, with a stratified log-rank p-value of 0.0001. The hazard ratio for the treatment effect was 0.58 (95 % CI: 0.43, 0.77). The two-year survival rates were 50.8 % in patients receiving azacitidine *versus* 26.2 % in patients receiving CCR ($p < 0.0001$).

The survival benefits of Vidaza were consistent regardless of the CCR treatment option (BSC alone, low-dose cytarabine plus BSC or standard induction chemotherapy plus BSC) utilised in the control arm.

When IPSS cytogenetic subgroups were analysed, similar findings in terms of median overall survival were observed in all groups (good, intermediate, poor cytogenetics, including monosomy 7). On analyses of age subgroups, an increase in median overall survival was observed for all groups (< 65 years, ≥ 65 years and ≥ 75 years).

Vidaza treatment was associated with a median time to death or transformation to AML of 13.0 months versus 7.6 months for those receiving CCR treatment, an improvement of 5.4 months with a stratified log-rank p-value of 0.0025.

Vidaza treatment was also associated with a reduction in cytopenias, and their related symptoms. Vidaza treatment led to a reduced need for red blood cell (RBC) and platelet transfusions. Of the patients in the azacitidine group who were RBC transfusion dependent at baseline, 45.0 % of these patients became RBC transfusion independent during the treatment period, compared with 11.4 % of the patients in the combined CCR groups (a statistically significant ($p < 0.0001$) difference of 33.6 % (95 % CI: 22.4, 44.6). In patients who were RBC transfusion dependent at baseline and became independent, the median duration of RBC transfusion independence was 13 months in the azacitidine group.

Response was assessed by the investigator or by the Independent Review Committee (IRC). Overall response (complete remission [CR] + partial remission [PR]) as determined by the investigator was 29 % in the azacitidine group and 12 % in the combined CCR group ($p = 0.0001$). Overall response (CR + PR) as determined by the IRC in AZA PH GL 2003 CL 001 was 7 % (12/179) in the azacitidine group compared with 1 % (2/179) in the combined CCR group ($p = 0.0113$). The differences between the IRC and investigator assessments of response were a consequence of the International Working Group (IWG) criteria requiring improvement in peripheral blood counts and maintenance of these improvements for a minimum of 56 days. A survival benefit was also demonstrated in patients that had not achieved a complete/partial response following azacitidine treatment. Haematological improvement (major or minor) as determined by the IRC was achieved in 49 % of patients receiving azacitidine compared with 29 % of patients treated with combined CCR ($p < 0.0001$).

In patients with one or more cytogenetic abnormalities at baseline, the percentage of patients with a major cytogenetic response was similar in the azacitidine and combined CCR groups. Minor cytogenetic response was statistically significantly ($p = 0.0015$) higher in the azacitidine group (34 %) compared with the combined CCR group (10 %).

Only patients with de novo disease were allowed entry into the AZA-001 study. Therefore it is not possible to assess whether there are any differences in the treatment effect between patients with de novo and secondary syndromes. The applicant committed to include patients with secondary syndromes in future studies.

Clinical safety

Azacitidine, a cytidine analogue that is incorporated into DNA and RNA, can be toxic to rapidly dividing cells, especially cells that form the haematopoietic system and mucosal tissue such as the gastrointestinal tract. Additional toxic effects can be expected due to the demethylating capacity of the active substance.

- Patient exposure

Although the total number of patients who received azacitidine in completed clinical MDS studies at the time of submission is limited to 449 patients (table 20), the body of safety information can be further enlarged by data from patients who have received azacitidine in presently ongoing studies (204 patients) and from the large number of patients who have received azacitidine and included in other data sources (approximately 26,938 patients). The combined estimated total of 27,591 patients provides an extensive experience with azacitidine.

Table 20 All completed studies - Overall extent of exposure to study treatment

	Number of patients					
	IV azacitidine	**SC azacitidine**	**BSC only**	**Low-dose cytarabine**	**Standard chemotherapy**	**Total**
Clinical pharmacology study						
AZA 2002 BA 002[b]	6	6	-	-	-	6
Controlled studies						
AZA-001	-	175	102	44	19	340
CALGB 9221	-	150[a]	92[c]	-	-	191
Uncontrolled studies						
CALGB 8921	-	70	-	-	-	70
CALGB 8421	48	-	-	-	-	48
All clinical studies	54[c]	401[c]	194[d]	44	19	655[c]

a Includes all patients exposed to azacitidine, including CALGB 9221 patients after crossing over from BSC only
b In Study AZA 2002 BA 002, crossover design
c Includes all 92 patients randomise to BSC of whom 51 patients who crossed over to azacitidine

In study AZA-001, of the 358 randomised patients, 340 patients received at least 1 dose of study drug and had at least 1 post-dose safety assessment (in the BSC-only group, safety evaluable patients received at least 1 post-randomisation safety assessment). Baseline FAB classifications as used in study AZA-001 were applied similarly in the CALGB studies in which most patients had an adjudicated baseline diagnosis of RAEB or RAEB-T except for study CALGB 9221 which also included patients with RA and RARS.

In study AZA-001, the majority of patients (86.3%, 151/175) remained on 75 mg/m^2 throughout the study and few patients required a reduction of their azacitidine dose. In the CALGB studies, increases up to 100 mg/m^2/day were allowed.

Patients with hepatic and renal dysfunction were excluded from the studies; therefore, there is limited information on these patient populations.

Patient exposure is presented in table 21.

Table 21 All completed studies - Patient exposure

	AZA-001				CALGB 8921/9221	CALGB 8421
	Azacitidine (N=175)	BSC only (N=102)	Low-dose cytarabine (N=44)	Standard chemotherapy (N=19)	All Azacitidine (N=220)	Azacitidine (N=48)
Cycles 1 or more	175 (100.0)	102 (100.0)	44 (100.0)	19 (100.0)	220 (100.0)	48 (100.0)
Cycles 2 or more	163 (93.1)	96 (94.1)	36 (81.8)	9 (47.4)	99 (45.0)	17 (35.4)
Cycles 3 or more	147 (84.0)	87 (85.3)	29 (65.9)	7 (36.8)	51 (23.2)	9 (18.8)
Cycles 4 or more	139 (79.4)	80 (78.4)	27 (61.4)	0	16 (7.3)	1 (2.1)
Cycles 6 or more	119 (68.0)	64 (62.7)	19 (43.2)	0		
Cycles 12 or more	63 (36.0)	23 (22.5)	5 (11.4)	0		
Cycles 24 or more	10 (5.7)	1 (1.0)	0	0		

The median prescribed dose of each of the standard chemotherapy drugs in both the induction and consolidation cycles was also consistent with the protocol: for cytarabine, 100 mg/m^2 for induction and 200 mg/m^2 for consolidation; and for daunorubicin, 60 mg/m^2 for both induction and consolidation; for idarubicin, 12 mg/m^2 for induction and 10.5 mg/m^2 for consolidation. Mean prescribed doses were similar to the medians with the exception of the mean prescribed dose for cytarabine during consolidation, 389.9 mg/m^2 (as the results of accidental overdose in one patient).

Adjustments in azacitidine dose occurred in 24 patients (13.7%) and in 22 patients (12.6%), toxicity lead to discontinuation of study treatment. Moreover, 82 (46.9%) patients had a dose interruption.

- Adverse events

Treatment-emergent adverse events (TEAE) in study AZA-001 are given in table 22.

Table 22 Study AZA-001 - Treatment-emergent adverse events with an incidence of ≥ 5.0%

	Any grade		Grade 3/4	
	Azacitidine (N=175)	BSC only (N=102)	Azacitidine (N=175)	BSC only (N=102)
Patients with at least 1 TEAE	**175 (100.0)**	**97 (95.1)**	**160 (91.4)**	**77 (75.5)**
Blood and lymphatic system disorders	156 (89.1)	68 (66.7)	143 (81.7)	48 (47.1)
Anaemia	90 (51.4)	45 (44.1)	24 (13.7)	9 (8.8)
Febrile neutropenia	24 (13.7)	10 (9.8)	22 (12.6)	7 (6.9)
Leucopenia	32 (18.3)*	2 (2.0)	26 (14.9)*	1 (1.0)
Neutropenia	115 (65.7)*	29 (28.4)	107 (61.1)*	22 (21.6)
Thrombocytopenia	122 (69.7)*	35 (34.3)	102 (58.3)*	29 (28.4)
Gastrointestinal disorders	142 (81.1)	49 (48.0)	26 (14.9)	9 (8.8)
Abdominal pain	22 (12.6)	7 (6.9)	7 (4.0)*	0
Abdominal pain upper	10 (5.7)	3 (2.9)	0	0
Constipation	88 (50.3)*	8 (7.8)	2 (1.1)	0
Diarrhoea	38 (21.7)	18 (17.6)	1 (0.6)	1 (1.0)
Dyspepsia	10 (5.7)*	2 (2.0)	0	0
Gingival bleeding	11 (6.3)	5 (4.9)	3 (1.7)*	0
Haemorrhoids	12 (6.9)	5 (4.9)	1 (0.6)*	0
Mouth ulceration	9 (5.1)	6 (5.9)	0	0
Nausea	84 (48.0)*	12 (11.8)	3 (1.7)*	0
Vomiting	47 (26.9)*	7 (6.9)	0	0
General disorders and administration site conditions	155 (88.6)	50 (49.0)	22 (12.6)	7 (6.9)
Asthenia	28 (16.0)	15 (14.7)	4 (2.3)	2 (2.0)
Chest pain	9 (5.1)	3 (2.9)	1 (0.6)	0
Oedema	9 (5.1)	5 (4.9)	1 (0.6)	0
Oedema peripheral	23 (13.1)	13 (12.7)	0	0
Fatigue	42 (24.0)*	12 (11.8)	6 (3.4)	2 (2.0)
Injection site bruising	9 (5.1)*	0	0	0
Injection site pain	33 (18.9)*	0	0	0
Injection site rash	10 (5.7)*	0	0	0
Injection site reaction	51 (29.1)*	0	1 (0.6)	0

	Any grade		Grade 3/4	
	Azacitidine (N=175)	**BSC only (N=102)**	**Azacitidine (N=175)**	**BSC only (N=102)**
Injection site erythema	75 (42.9)*	0	0	0
Injection site haematoma	11 (6.3)*	0	0	0
Injection site induration	9 (5.1)*	0	0	0
Pyrexia	53 (30.3)	18 (17.6)	8 (4.6)	1 (1.0)
Nervous system disorders	69 (39.4)	22 (21.6)	16 (9.1)	9 (8.8)
Dizziness	17 (9.7)	7 (6.9)	1 (0.6)	0
Headache	25 (14.3)	8 (7.8)	0	0
Lethargy	13 (7.4)*	2 (2.0)	0	1 (1.0)
Psychiatric disorders	41 (23.4)*	5 (4.9)	7 (4.0)*	1 (1.0)
Anxiety	9 (5.1)*	1 (1.0)	0	0
Depression	10 (5.7)	3 (2.9)	1 (0.6)	0
Insomnia	15 (8.6)*	3 (2.9)	0	0
Renal and urinary disorders	26 (14.9)	12 (11.8)	8 (4.6)	4 (3.9)
Haematuria	11 (6.3)*	2 (2.0)	4 (2.3)*	1 (1.0)
Respiratory, thoracic and mediastinal disorders	95 (54.3)	37 (36.3)	22 (12.6)	10 (9.8)
Cough	34 (19.4)	15 (14.7)	1 (0.6)	0
Dyspnoea	26 (14.9)*	5 (4.9)	6 (3.4)	2 (2.0)
Dyspnoea exertional	9 (5.1)*	1 (1.0)	0	0
Epistaxis	29 (16.6)	16 (15.7)	9 (5.1)	7 (6.9)
Pharyngolaryngeal pain	11 (6.3)*	3 (2.9)	0	0
Skin and subcutaneous tissue disorders	96 (54.9)	20 (19.6)	5 (2.9)*	0
Erythema	13 (7.4)*	3 (2.9)	0	0
Petechiae	20 (11.4)*	4 (3.9)	2 (1.1)	0
Pruritus	21 (12.0)*	2 (2.0)	0	0
Rash	18 (10.3)*	1 (1.0)	0	0
Vascular disorders	52 (29.7)	20 (19.6)	9 (5.1)	4 (3.9)
Haematoma	21 (12.0)	10 (9.8)	0	0
Hypertension	15 (8.6)*	4 (3.9)	2 (1.1)	2 (2.0)
Hypotension	10 (5.7)	3 (2.9)	3 (1.7)	1 (1.0)
Infections and infestations	134 (76.6)	56 (54.9)	52 (29.7)	22 (21.6)
Bronchitis	17 (9.7)	8 (7.8)	0	0
Influenza	10 (5.7)	5 (4.9)	0	0
Nasopharyngitis	33 (18.9)	13 (12.7)	2(1.1)	0
Oral candidiasis	11 (6.3)	5 (4.9)	1 (0.6)	0
Oral herpes	17 (9.7)	5 (4.9)	1 (0.6)	0
Pneumonia	22 (12.6)	12 (11.8)	18 (10.3)	8 (7.8)
Rhinitis	10 (5.7)*	1 (1.0)	0	0
Upper respiratory tract infection	16 (9.1)8	4 (3.9)	3 (1.7)	0
Urinary tract infection	15 (8.6)*	3 (2.9)	3 (1.7)	0
Musculoskeletal and connective tissue disorders	60 (34.3)	31 (30.4)	8 (4.6)	6 (5.8)
Arthralgia	15 (8.6)	8 (7.8)	1 (0.6)	2 (2.0)
Back pain	15 (8.6)	8 (7.8)	1 (0.6)	3 (3.0)
Muscle spasm	10 (5.7)	5 (4.9)	0	0
Musculoskeletal chest pain	9 (5.1)	3 (2.9)	0	0
Pain in the extremity	11 (6.3)	5 (4.9)	1 (0.6)	1 (1.0)
Injury, poisoning and procedural complications	56 (32.0)	16 (15.7)	6 (3.4)	5 (4.9)
Contusion	14 (8.0)	5 (4.9)	0	1 (1.0)
Transfusion reactions	21 (12.0)*	5 (4.9)	4 (2.3)	1 (1.0)
Metabolism and nutrition disorders	55 (31.4)	25 (24.5)	14 (8.0)	7 (6.9)
Anorexia	25 (14.3)	9 (8.8)	3 (1.7)	0
Hypokalaemia	11 (6.3)*	3 (2.9)	3 (1.7)	3 (2.9)
Neoplasms benign, malignant and unspecified	44 (25.1)	40 (39.2)	22 (12.5)	16 (15.7)
Acute myeloid leukaemia	30 (17.1)	36 (35.3)	28 (16.0)	32 (31.4)
Reproductive system and breast disorders	9 (5.1)	5 (4.9)	1 (0.6)	1 (1.0)
Cardiac disorders	39 (22.3)	19 (18.6)	15 (8.6)	12 (11.8)
Eye disorders	38 (21.7)	7 (6.9)	9 (5.1)	0
Investigations	38 (21.7)	11 (10.8)	13 (7.4)	1 (1.0)
Weight decreased	14 (8.0)*	0	1 (0.6_	0
Ear and labyrinth disorders	15 (8.6)	9 (8.8)	2 (1.1)	0

	Any grade		Grade 3/4	
	Azacitidine (N=175)	**BSC only (N=102)**	**Azacitidine (N=175)**	**BSC only (N=102)**
Hepatobiliary disorders	9 (5.1)	1 (1.0)	4 (2.3)	0

* Indicates 2-fold greater frequency in the azacitidine group compared with the best supportive care group

The most frequently reported TEAE for patients receiving azacitidine in the CALGB studies were anaemia, nausea and thrombocytopenia (within study CALGB 9221, the percentage of event of anaemia was similar to that of the BSC group). System organ classes (SOC) were similar in studies CALGB 8921/9221 (SC) and CALGB 8421 (IV), except for skin and subcutaneous tissue disorders which were more frequent in study 8421.

In an analysis of TEAE by cycle onset for azacitidine in study AZA-001, findings suggested that the first occurrence of events of thrombocytopenia, neutropenia, anaemia, constipation, nausea, injection site erythema and injection site reaction were reported most often in Cycles 1 and 2; this was consistent in the CALGB studies. The most common events (> 20.0%) reported in the azacitidine group during Cycles 1 and 2 included those generally associated with the known effects of this drug: thrombocytopenia (54.3%), neutropenia (50.3%), constipation (35.4%), nausea (35.4%), injection site erythema (34.9%), anaemia (32.6%) and injection site reaction (20.6%); by Cycles 5 and 6, the percentages of these events ranged from 0 (nausea) to 6.9% (anaemia). Within the cycle, the first occurrence of the haematology events (thrombocytopenia, neutropenia, and anaemia) occurred most often within the first 3 weeks of the cycle in these studies. Events typically associated with administration of azacitidine, including nausea, vomiting, constipation, and injection site erythema/reaction/pain, occurred within the first week of the cycle, coinciding with the days of treatment.

When TEAE were summarised by dose in studies AZA-001 and CALGB, events of neutropenia, anaemia, nausea, vomiting, constipation and injection site reactions tended to be reported at increasing frequencies at higher doses of azacitidine. In study AZA-001, this tendency was also present with the reporting of events of thrombocytopenia.

The most frequent treatment-related events in the azacitidine treatment group are consistent with those most often reported from the all TEAEs and listed in the SmPC. The treatment-related events between the treatment groups are also consistent. All of the TEAEs listed are either known effects of the active substances used in the study or were associated with the SC administration of azacitidine (injection site erythema/reaction/pain).

In study AZA-001, there were no patients that had their dose of azacitidine reduced, interrupted or discontinued due to renal toxicities. However, abnormalities in hepatic function lead to treatment interruption and increased circulating enzymes lead to dose reduction.

- Serious adverse event/deaths/other significant events

The number of deaths and causes of death that occurred on-treatment and post-treatment are provided in table 23.

Table 23 Study AZA-001 - Deaths

		Conventional Care Regimens		
	Azacitidine (N=175)	**BSC only (N=102)**	**Low-dose cytarabine (N=44)**	**Standard chemotherapy (N=19)**
Number of on-treatment deaths[a]	**21 (12.0)**	**19 (18.6)**	**6 (13.6)**	**0**
Disease progression	5 (2.9)	3 (2.9)	2 (4.5)	
Acute myeloid leukaemia	2 (1.1)	1 (1.0)	0	0
Myelodysplastic syndrome	3 (1.7)	2 (2.0)	2 (4.5)	0
Other				
Blood and lymphatic system disorders	2 (1.1)	0	0	0
Infections and infestations	8 (4.6)	4 (3.9)	4 (9.1)	0
Haemorrhage	5 (2.9)	7 (6.9)	0	0
Cardiac disorders	3 (1.7)	3 (2.9)	0	0
General disorders and administration site conditions	1 (0.6)	2 (2.0)	0	0
Nervous system disorders excluding haemorrhage events	1 (0.6)	0	1 (2.3)	0
Renal and urinary disorders	0	2 (2.0)	1 (2.3)	0
Respiratory, thoracic and mediastinal disorders	6 (3.4)	2 (2.0)	1 (2.3)	0
Vascular disorders	0	1 (1.0)	0	0
Number of post-treatment deaths	**58 (33.1)**	**44 (43.1)**	**20 (45.5)**	**15 (78.9)**
Disease progression	27 (15.4)	14 (13.7)	11 (25.0)	9 (47.4)
Acute leukaemia	0	0	0	1 (5.3)
Acute myeloid leukaemia	21 (12.0)	10 (9.8)	4 (9.1)	4 (21.1)
Blast crisis in myelogenous leukaemia	1 (0.6)	0	0	0
Leukaemia	0	0	1 (2.3)	0
Leukaemia monocytic	0	0	0	1 (5.3)
Myelodysplastic syndrome	5 (2.9)	4 (3.9)	6 (13.6)	3 (15.8)
Other				
Blood and lymphatic system disorders	3 (1.7)	4 (3.9)	0	0
Infections and infestations	17 (9.7)	12 (11.8)	4 (9.1)	6 (31.6)
Haemorrhage	5 (2.9)	6 (5.9)	3 (6.8)	1 (5.3)
Cardiac disorders	5 (2.9)	5 (4.9)	1 (2.3)	1 (5.3)
Gastrointestinal disorders exclude haemorrhage events	0	1 (1.0)	0	0
General disorders and administration site conditions	6 (3.4)	5 (4.9)	1 (2.3)	1 (5.3)
Hepatobiliary disorders	1 (0.6)	0	0	0
Immune system disorders	1 (0.6)	0	0	0
Injury, poisoning and procedural complications - modified to exclude haemorrhage events	2 (1.1)	1 (1.0)	0	0
Metabolism and nutrition disorders	3 (1.7)	1 (1.0)	1 (2.3)	0
Neoplasms benign, malignant and unspecified excluding disease progression	4 (2.3)	0	1 (2.3)	0
Nervous system disorders excluding haemorrhage events	3 (1.7)	1 (1.0)	0	0
Renal and urinary disorders	2 (1.1)	1 (1.0)	0	0
Respiratory, thoracic and mediastinal disorders	3 (1.7)	1 (1.0)	0	0
Vascular disorders excluding haemorrhage events	1 (0.6)	0	0	0

a Patients could have more than 1 cause of death. "On-treatment" is defined as occurring from the first dose until 42 days after the last dose of azacitidine and low-dose cytarabine, until 70 days after the last dose of standard chemotherapy, or between randomisation and the final visit for BSC.

The frequency of patients with serious adverse events (SAE) other than deaths in study AZA-001 is summarised for events that occurred in > 2 patients in the azacitidine group in table 24.

Table 24 Study AZA-001 – Serious Adverse Events

		Conventional Care Regimens		
	Azacitidine (N=175)	**BSC only (N=102)**	**Low-dose cytarabine (N=44)**	**Standard chemotherapy (N=19)**
Patients with at least 1 serious TEAE other than death[a]	**104 (59.4)**	**61 (59.8)**	**24 (54.5)**	**13 (68.4)**
Blood and lymphatic system disorders	35 (20.0)	9 (8.8)	7 (15.9)	6 (31.6)
Anaemia	12 (6.9)	3 (2.9)	2 (4.5)	1 (5.3)
Febrile neutropenia	18 (10.3)	3 (2.9)	1 (2.3)	5 (26.3)
Neutropenia	5 (2.9)	0	0	1 (5.3)
Thrombocytopenia	8 (4.6)	2 (2.0)	2 (4.5)	1 (5.3)
General disorders and administration site conditions	16 (9.1)	4 (3.9)	8 (18.2)	1 (5.3)
Pyrexia	10 (5.7)	3 (2.9)	5 (11.4)	0
Infections and infestations	44 (25.1)	23 (22.5)	11 (25.0)	9 (47.4)
Bronchopneumonia	3 (1.7)	3 (2.9)	0	0
Neutropenic sepsis	4 (2.3)	1 (1.0)	1 (2.3)	2 (10.5)
Pneumonia	13 (7.4)	10 (9.8)	2 (4.5)	2 (10.5)
Urinary tract infection	5 (2.9)	0	2 (4.5)	1 (5.3)
Injury, poisoning and procedural complications	7 (4.0)	1 (1.0)	2 (4.5)	0
Transfusion reaction	3 (1.7)	0	1 (2.3)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	28 (16.0)	24 (23.5)	4 (9.1)	0
Acute myeloid leukemia	22 (12.6)	24 (23.5)	3 (6.8)	0
Respiratory, thoracic and mediastinal disorders	9 (5.1)	7 (6.9)	3 (6.8)	1 (5.3)
Epistaxis	4 (2.3)	3 (2.9)	2 (4.5)	0

a Multiple reports of the same preferred term or system organ class for a patient are counted only once within each treatment group

- Laboratory findings

Consistent with the TEAE and efficacy analyses in study AZA-001, analyses of haematology parameters over time confirmed that azacitidine has an effect on haematologic parameters. The median time to nadir values across haematology parameters was 14 to 15 days for patients treated with azacitidine (compared with 17 to 21 days for patients treated with low-dose cytarabine and 17 to 23 days for patients treated with standard chemotherapy). The reduction in haemoglobin and platelets diminished over time due to the cytotoxic effect of azacitidine. The median haemoglobin values in patients treated with azacitidine improved over time, an effect that was not evident with BSC-only.

Laboratory analyses of chemistry data in study AZA-001, including electrolytes and measures of hepatic and renal function, showed that even after prolonged administration, azacitidine had no effects on renal or liver function and had only very minor effects on electrolytes over time, which were also evident in the BSC-only group. Hyperbilirubinaemia was reported in 3 patients in the azacitidine treatment group (3/175), but not in the other treatment groups. All of these events were reported within the first 3 cycles, and were either Grade 2 or Grade 3 events. In one patient this hyperbilirubinaemia appeared unresolved.

The CALGB studies showed similar results.

- Safety in special populations

No specific studies have been conducted in hepatic and renal impairment, pregnancy and lactation, or in children and adolescent. However, TEAE were analysed by age, gender, baseline creatinine, albumin, bilirubin and FAB, WHO and IPSS.

In the azacitidine group, similar percentages of individual TEAEs were noted for the majority of TEAEs across the age categories. Although there are 2-fold differences in the frequencies of individual TEAEs between the older age groups (≥ 65 years or ≥ 75 years) compared with < 65 years in the azacitidine group, there does not appear to be any clinically relevant differences based on age.

Also, with regard to gender, although there are 2-fold differences in the frequencies of individual TEAEs between males and females in the azacitidine group, there does not appear to be any clinically relevant differences based on gender.

- Safety related to drug-drug interactions and other interactions

No drug interaction studies have been performed.

- Discontinuation due to adverse events

In Study AZA-001, the overall percentage of patients with a TEAE leading to discontinuation of azacitidine and BSC were 12.6% (22/175) and 3.9% (4/102) respectively. In the CALGB studies, the overall percentage ranged from 18.0 to 31.3%. In the MDS studies, the most common reason for discontinuation of azacitidine was due to haematological TEAEs (occurring in < 5% of patients). In Study AZA-001, no patient discontinued study treatment due to any of the common non haematological toxicities (i.e., nausea/vomiting or injection site reactions).

Treatment was not discontinued in any patient in clinical pharmacology study.

- Post-marketing experience

From a review on data from other additional clinical studies, from compassionate-use, from post-marketing data, most frequently reported AE were haematological (thrombocytopenia, neutropenia, febrile neutropenia), gastrointestinal events (nausea, vomiting, constipation, diarrhoea) and injection site reactions (erythema, pain, bruising).

Most often causes of death were due to haematological toxicity, infectious complications and bleeding.

Hepatic and renal adverse events were reported infrequently. However, based on early investigations with azacitidine in combination with other cytotoxic agents or at higher doses, renal abnormalities, including elevated serum creatinine, renal tubular acidosis and renal failure were reported. Published reports also described an association between azacitidine and hepatic fatal failure in patients with solid tumours and hepatic metastasis, especially those with albumin < 30 g/l.

- Discussion on clinical safety

Vidaza treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting.

Vidaza is contraindicated in the following situations: Known hypersensitivity to the active substance or to any of the excipients, advanced malignant hepatic tumours (see SPC section 4.4), or lactation (see SPC section 4.6).

Adverse reactions considered to be possibly or probably related to the administration of Vidaza have occurred in 97 % of patients. The most commonly reported adverse reactions with azacitidine treatment were haematological reactions (71.4 %) including thrombocytopenia, neutropenia and leukopenia (usually Grade 3-4), gastrointestinal events (60.6 %) including nausea, vomiting (usually Grade 1-2) or injection site reactions (77.1 %; usually Grade 1-2).

The most common serious adverse reactions (> 2 %) noted from the pivotal study (AZA PH GL 2003 CL 001) and also reported in the supporting studies (CALGB 9221 and CALGB 8921) included febrile neutropenia (8.0 %) and anaemia (2.3 %). Other less frequently reported serious adverse reactions (< 2 %) included neutropenic sepsis, pneumonia, thrombocytopenia and haemorrhagic events (e.g. cerebral haemorrhage).

Haematologic adverse reactions

The most commonly reported adverse reactions associated with azacitidine treatment were haematological including thrombocytopenia, neutropenia and leukopenia, and were usually Grade 3 or 4. There is a greater risk of these events occurring during the first 2 cycles, after which they occur with less frequency in patients with restoration of haematological function. Most haematological adverse reactions were managed by routine monitoring of complete blood counts and delaying azacitidine administration in the next cycle, prophylactic antibiotics and/or growth factor support (e.g. G-CSF) for neutropenia and transfusions for anaemia or thromobocytopenia as required.

Infections

Myelosuppression may lead to neutropenia and an increased risk of infection. Serious adverse reactions such as neutropenic sepsis (0.8 %) and pneumonia (2.5 %) were reported in patients receiving azacitidine. Infections may be managed with the use of anti-infectives plus growth factor support (e.g. G-CSF) for neutropenia.

Bleeding

Bleeding may occur with patients receiving azacitidine. Serious adverse reactions such as gastrointestinal haemorrhage (0.8 %) and intracranial haemorrhage (0.5 %) have been reported. Patients should be monitored for signs and symptoms of bleeding, particularly those with pre-existing or treatment-related thrombocytopenia.

Hypersensitivity

Serious hypersensitivity reactions (0.25 %) have been reported in patients receiving azacitidine. In case of an anaphylactic-like reaction, treatment with azacitidine should be immediately discontinued and appropriate symptomatic treatment initiated. The majority of skin and subcutaneous adverse reactions were associated with the injection site. None of these adverse reactions led to temporary or permanent discontinuation of azacitidine, or reduction of azacitidine dose in the pivotal study. The majority of adverse reactions occurred during the first 2 cycles and tended to decrease with subsequent cycles. Subcutaneous adverse reactions such as injection site rash/inflammation/pruritus, rash, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs).

Gastrointestinal adverse reactions

The most commonly reported gastrointestinal adverse reactions associated with azacitidine treatment included constipation, diarrhoea, nausea and vomiting. These adverse reactions were managed symptomatically with anti-emetics for nausea and vomiting; antidiarrhoeals for diarrhoea, and laxatives and/or stool softeners for constipation.

Overdose

One case of overdose with azacitidine was reported during clinical trials. A patient experienced diarrhoea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose. In the event of overdose, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for azacitidine overdose.

Special Populations

Renal impairment: No formal studies have been conducted in patients with decreased renal function. Patients with severe organ impairment should be carefully monitored for adverse events. No specific modification to the starting dose is recommended in patients with renal impairment (e.g. baseline serum creatinine or blood urea nitrogen [BUN] ≥ 2-fold above upper limit of normal [ULN] or serum bicarbonate less than 20 mmol/l) prior to starting treatment; subsequent dose modifications should be based on haematology and renal laboratory values. If unexplained reductions in serum bicarbonate levels to less than 20 mmol/l occur, the dose should be reduced by 50 % on the next cycle. If unexplained elevations in serum creatinine or BUN to ≥ 2-fold above baseline values and above ULN occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50 % on the next treatment cycle (see SPC section 4.4).

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported rarely in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/l in association with an alkaline urine and hypokalaemia (serum potassium < 3 mmol/l) developed in 5 subjects with chronic myelogenous leukaemia (CML) treated with azacitidine and etoposide.

Patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney (see SPC section 4.2).

Hepatic impairment: No formal studies have been conducted in patients with hepatic impairment (see SPC section 4.4). Patients with severe hepatic organ impairment should be carefully monitored for

adverse events. No specific modification to the starting dose is recommended for patients with hepatic impairment prior to starting treatment; subsequent dose modifications should be based on haematology laboratory values. Patients with extensive tumour burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline serum albumin < 30 g/l. Vidaza is contraindicated in patients with advanced malignant hepatic tumours (see SPC sections 4.3 and 4.4).

Elderly: No specific dose adjustments are recommended for the elderly. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Children and adolescents: Vidaza is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Laboratory tests

Liver function tests and serum creatinine should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.

Method of administration

Reconstituted Vidaza should be injected subcutaneously into the upper arm, thigh or abdomen.

Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site

and never into areas where the site is tender, bruised, red, or hardened.

Haematological toxicity

Treatment with azacitidine is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles (see SPC section 4.8). Complete blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle. After administration of the recommended dose for the first cycle, the dose for subsequent cycles should be reduced or its administration delayed based on nadir counts and haematological response (see SPC section 4.2). Patients should be advised to promptly report febrile episodes. Patients and physicians are also advised to be observant for signs and symptoms of bleeding.

Cardiac and pulmonary disease

Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal clinical study and therefore the safety and efficacy of Vidaza in these patients has not been established.

Pregnancy

There are no adequate data on the use of azacitidine in pregnant women. Studies in mice have shown reproductive toxicity (see SPC section 5.3). The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, azacitidine should not be used during pregnancy, especially during the first trimester, unless clearly necessary. The advantages of treatment should be weighed against the possible risk for the foetus in every individual case. Men and women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Lactation

It is not known whether azacitidine or its metabolites are excreted in human milk. Due to the potential serious adverse reactions in the nursing child, breast-feeding is contraindicated during azacitidine therapy.

Fertility

There are no human data on the effect of azacitidine on fertility. In animals, adverse effects of azacitidine on male fertility have been documented (see SPC section 5.3). Men should be advised not to father a child while receiving treatment and must use effective contraception during and up to 3 months after treatment. Before starting treatment, male patients should be advised to seek counseling on sperm storage.

No studies of the effects on the ability to drive and use machines have been performed. Patients should be advised that they may experience undesirable effects such as fatigue, during treatment. Therefore, caution should be recommended when driving a car or operating machines.

Adequate special precautions for disposal and other handling are provided in the SPC (see section 6)

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Myelosuppression	• Routine pharmacovigilance - Analysis of adverse events in PSURs. - Specific adverse event collection form.	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations on dose adjustments and delay based on haematology laboratory values to reduce the risk. - Section 4.4 of the SPC – Warnings regarding haematotoxicity and how to monitor this risk. - Section 4.8 of the SPC - Listed as ADRs and details on the frequency and severity for thrombocytopenia, neutropenia and leukopenia
Hemorrhagic events	• Routine pharmacovigilance - Analysis of adverse events in PSURs. - Specific adverse event collection form	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations on dose adjustments and delay based on haematology laboratory values including platelet count, to reduce the risk. - Section 4.4 of the SPC – Warnings regarding thrombocytopenia and how to monitor this risk. - Section 4.8 of the SPC - Details on hemorrhagic ADRs.
Infections	• Routine pharmacovigilance - Analysis of adverse events in PSURs. - Specific adverse event collection form.	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations on dose adjustments and delay based on haematology laboratory values including ANC, to reduce the risk. - Section 4.4 of the SPC – Warnings regarding neutropenia and how to monitor this risk. - ADRs of infections listed in Section 4.8 of the SPC.
Renal and urinary events	• Routine pharmacovigilance - Analysis of adverse events in PSURs. - Specific adverse event collection	• Routine risk minimization activities - Sections 4.2 of the SPC - Recommendations on dose adjustments based on renal function and serum

	form. • Additional pharmacovigilance - Clinical study in renal impairment.	electrolytes. - Section 4.4 of the SPC – Warnings regarding renal abnormalities. - Listed as ADRs in Section 4.8 of the SPC.
Gastrointestinal events	• Routine pharmacovigilance	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations for routine antiemetic therapy to prevent and manage this risk. - Listed as ADRs in Section 4.8 of the SPC.
Hepatic events	• Routine pharmacovigilance - Analysis of adverse events in PSURs. - Specific adverse event collection form.	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations for monitoring liver chemistries and for monitoring patients with severe hepatic organ impairment. - Section 4.3 of the SPC – Contraindication in patients with advanced malignant hepatic tumors. - Section 4.4 of the SPC - Warning in patients with severe hepatic impairment.
Injection site reactions	• Routine pharmacovigilance - Analysis of adverse events in PSURs. - Specific adverse event collection form.	• Routine risk minimization activities - Section 4.2 of the SPC - Advice for SC administration. - Injection site reactions listed in the SPC, Section 4.8.
Potential risks		
Psychiatric disorders	• Routine pharmacovigilance - Analysis of adverse events in PSURs.	• Routine risk minimization activities - Listed as ADRs in section 4.8 of the SPC.
Malignancies (including injection site tumors)	• Routine pharmacovigilance - Analysis of adverse events in PSURs.	• Routine risk minimization activities - Studies have shown that azacitidine is carcinogenic and mutagenic in rats and mice (section 5.3 of the SPC).
Off-label Use (in adults, including low-risk MDS patients, and children)	• Routine pharmacovigilance - Data regarding the indication, including the risk category of MDS patients, will be provided and analyzed for the reported adverse events in PSURs. - Sales data will be analyzed and a comparison made with the projected post-authorization usage.	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations for initiation and monitoring of azacitidine treatment under the supervision of a physician experienced in the use of chemotherapeutic agents. Indicates that azacitidine is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.
Neurological events and muscle weakness	• Routine pharmacovigilance - Analysis of adverse events in PSURs.	• Routine risk minimization activities - Listed as ADRs in section 4.8 of the SPC.
Male infertility	• Routine pharmacovigilance - Analysis of adverse events in	• Routine risk minimization activities - section 4.6 of the SPC - Before starting

	PSURs.	treatment, male patients should be advised to seek counseling on sperm storage.
Medication errors	• Routine pharmacovigilance - Analysis of reports of medication errors in PSURs.	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations for initiation and monitoring of treatment under the supervision of a physician experienced in the use of chemotherapeutic agents. - Section 6.6 of the SPC - Provides detailed instructions for reconstitution and administration procedures.
Missing Information		
Use in renal impairment	• Routine pharmacovigilance - Analysis of adverse events in patients with renal impairment in PSURs. - Specific adverse event collection form. Additional pharmacovigilance - Clinical study in renal impairment.	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations for monitoring adverse events in patients with severe renal impairment. - Section 4.4 of the SPC - Warning for patients with severe renal impairment.
Use in hepatic impairment	• Routine pharmacovigilance - Analysis of adverse events in PSURs. - Specific adverse event collection form.	• Routine risk minimization activities - Section 4.2 of the SPC - Recommendations for monitoring adverse events in patients with severe hepatic impairment. - Section 4.3 of the SPC -Contraindication in patients with advanced malignant hepatic tumors. - Section 4.4 of the SPC - Warning for patients with severe hepatic impairment.
Use in cardiac impairment	• Routine pharmacovigilance - Analysis of adverse events in patients with cardiac impairment in PSURs.	• Routine risk minimization activities - Section 4.4 of the SPC - Warning for patients with cardiac impairment.
Interactions with other drugs (including cytotoxics)	• Routine pharmacovigilance - Analysis of identified interactions in PSURs.	• Routine risk minimization activities - Section 4.5 and 5.2 of the SPC - Details of potential interactions
Pregnancy and lactation	• Routine pharmacovigilance - Analysis of pregnancy and lactation cases in PSURs.	• Routine risk minimization activities - Section 4.6 of the SPC - Azacitidine should not be used during pregnancy unless clearly necessary. - Due to the potential serious adverse reactions in the nursing child, breastfeeding is contraindicated during azacitidine therapy (sections 4.3 and 4.6 of the SPC).
Use in elderly patients	• Routine pharmacovigilance - Analysis of adverse events in	• Routine risk minimization activities - section 4.2 of the SPC –

affected by renal impairment	elderly patients with renal impairment in PSURs. • Additional pharmacovigilance - Clinical study in patients with renal impairment.	Recommendation for monitoring renal function in elderly patients.
Use in children	• Routine pharmacovigilance - Analysis of adverse events in pediatric patients in PSURs.	• Routine risk minimization activities - section 4.2 of the SPC - Indicates that azacitidine is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues which might have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Azacitidine induces both gene mutations and chromosomal aberrations in bacterial and mammalian cell systems in vitro. The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumours of the haematopoietic system in female mice, when administered intraperitoneally 3 times per week for 52 weeks. An increased incidence of tumours in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine administered intraperitoneally for 50 weeks. A tumorigenicity study in rats revealed an increased incidence of testicular tumours.

Early embryotoxicity studies in mice revealed a 44 % frequency of intrauterine embryonal death (increased resorption) after a single intraperitoneal injection of azacitidine during organogenesis.

Developmental abnormalities in the brain have been detected in mice given azacitidine on or before closure of the hard palate. In rats, azacitidine caused no adverse effects when given pre-implantation, but it was clearly embryotoxic during when given during organogenesis. Foetal abnormalities caused during organogenesis included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (micrognathia, gastroschisis, oedema, and rib abnormalities).

Administration of azacitidine to male mice prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats resulted in decreased weight of the testes and epididymides, decreased sperm counts, decreased pregnancy rates, an increase in abnormal embryos and increased loss of embryos in mated females (see SPC section 4.4).

Efficacy

The clinical efficacy of Vidaza was studied in a multicenter randomised Phase 3 comparative study. Azacitidine plus best supportive care (BSC) (n = 179) was compared to conventional care regimens (CCR). CCR consisted of BSC alone (n = 105), low-dose cytarabine plus BSC (n = 49) or standard induction chemotherapy plus BSC (n = 25). The primary endpoint of the study was overall survival. Vidaza was administered at a subcutaneous (s.c.) dose of 75 mg/m$_2$ daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle) for a median of 9 cycles (range = 1-39) and a mean of 10.2 cycles. In the ITT analysis of 358 patients (179 azacitidine and 179 CCR), Vidaza treatment was

associated with a median survival of 24.46 months *versus* 15.02 months for those receiving CCR treatment, a difference of 9.4 months, with a stratified log-rank p-value of 0.0001. The hazard ratio for the treatment effect was 0.58 (95 % CI: 0.43, 0.77). The two-year survival rates were 50.8 % in patients receiving azacitidine *versus* 26.2 % in patients receiving CCR ($p < 0.0001$).

Safety

Adverse reactions considered to be possibly or probably related to the administration of Vidaza have occurred in 97 % of patients.

The most commonly reported adverse reactions with azacitidine treatment were haematological reactions (71.4 %) including thrombocytopenia, neutropenia and leukopenia (usually Grade 3-4), gastrointestinal events (60.6 %) including nausea, vomiting (usually Grade 1-2) or injection site reactions (77.1 %; usually Grade 1-2).

The most common serious adverse reactions (> 2 %) noted from the pivotal study (AZA PH GL 2003 CL 001) and also reported in the supporting studies (CALGB 9221 and CALGB 8921) included febrile neutropenia (8.0 %) and anaemia (2.3 %). Other less frequently reported serious adverse reactions (< 2 %) included neutropenic sepsis, pneumonia, thrombocytopenia and haemorrhagic events (e.g. cerebral haemorrhage).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product. No additional risk minimisation activities were required beyond those included in the product information.

- User consultation

The Patient Information Leaflet (PIL) for Vidaza (azacitidine) has been tested in English in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. The PIL for Vidaza (azacitidine) was found to contain all the necessary information in a way that is accessible and understandable to those who participated in this test.

It is considered that the tested PIL meets the requirements set for User Testing.

Risk-benefit assessment

The present assessment of the MAA of azacitidine for the proposed indications in MDS and AML was based on the pivotal study AZA-001 in addition to the earlier submitted CALGB studies.

The design of pivotal study AZA-001 was considered appropriate to investigate the benefits of azacitidine for the currently proposed indications: patients with intermediate-2 or high risk MDS, CMML (according to IPSS) and AML with 20%-30% blasts and multilineage dysplasia (WHO). Overall results from the AZA-001 study showed that patients in the azacitidine arm, when compared with patients with similar clinical characteristics that were treated with currently appropriate therapy, had a survival benefit. Therefore, the primary endpoint was met and the difference in OS can be regarded clinically relevant. The results regarding the secondary endpoints are in line with the survival benefit. The safety profile of azacitidine is considered acceptable. The toxicity of azacitidine is consistent with that observed in general from a cytidine analogue, an antimetabolite. The most prominent toxicity consisted of myelotoxicity which translated into symptomatic anaemia and, more important, leucopenia and thrombocytopenia. In conclusion, the efficacy of azacitidine can be considered established and the safety profile is acceptable in the claimed indication, and the CHMP considers that the benefit risk balance is positive.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Vidaza is not similar to Trisenox or Glivec within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Vidaza for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with: intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS), chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder, or acute myeloid leukaemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification, was favourable and therefore recommended the granting of the marketing authorisation.

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