2 SYNOPSIS

Name of Sponsor/Company: Pharmion Corporation **Name of Finished Product:** **Name of Active Ingredient:**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*

Title of Study: 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) (Protocol AZA PH GL 2003 CL 001)

Investigator(s): International/Multicenter

Study Center(s): 79 investigative sites

Publication (Reference): Fenaux P, Mufti GJ, Santini V, Finelli C, Giagounidis A, Schoch R, et al. Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): Results of the AZA-001 Phase III study. [Abstract 817]. *Blood* 2007;110(11).

Study Period: 24 November 2003 (first patient's informed consent) to 24 July 2007 (last patient's last follow-up visit)	**Phase of development:** 3

Objectives:

Primary:

- To determine the effect of azacitidine plus best supportive care (BSC), as compared with conventional care regimens (CCR) plus BSC, in survival in MDS patients.

Secondary:

- Time to acute myeloid leukemia (AML) transformation or death from any cause;
- Time to transformation to AML, censored at death;
- Hematologic status and episodes of infections requiring intravenous antibiotics (antibacterial or antifungal) or antivirals;
- Time to relapse after complete remission (CR) or partial remission (PR), or disease progression (according to International Working Group [IWG] criteria), censored at death;
- Safety and toxicity of azacitidine plus BSC; and
- Pharmacoeconomic differences in MDS patients treated with azacitidine plus BSC, as compared with patients receiving CCR plus BSC (results will be provided in a separate report).

Methodology: This was an international, multicenter, controlled, open-label, randomized, parallel-group, comparative study conducted in MDS patients (diagnosed with refractory anemia with excess blasts (RAEB) or refractory anemia with excess blasts in transformation (RAEB-T) (French-American-British [FAB] classification), or chronic myelomonocytic leukemia (CMMoL) (modified FAB classification) with a high risk of death. Eligible patients were randomized at a ratio of 1:1 to either azacitidine treatment or conventional care treatment. The conventional care treatment regimen consisted of 3 options, one of which was to be assigned to the patient by the investigator: BSC alone, low-dose cytarabine, or standard

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chemotherapy. Treatment options in the conventional care regimens were assigned based on local practice and on the evaluation of the patient's underlying disease condition at the time of screening. The intended treatment selection from the conventional care regimens was to be recorded for all patients prior to randomization to either azacitidine or conventional care treatment. All patients, regardless of randomized treatment, were to receive BSC. Patients were not permitted to cross over between any of the treatment groups during the study. The treatment regimen was to be continued until patient discontinuation. Patients **could** be discontinued due to relapse after CR or PR or disease progression, and then treated per investigator discretion; but discontinuation was **mandatory** if the patient withdrew consent, if the patient experienced unacceptable toxicity, or if bone marrow blast count was > 30% and at least 50% increased from pretreatment blast count. For patients experiencing toxicities, treatment regimens other than BSC only could be modified by modifying the dose or delaying the next treatment cycle (depending on which treatment was received). All discontinued patients were to be followed for 28 days following the date of final scheduled study visit for collection of adverse events. Patients in the follow-up period were followed until the end of the study for MDS/AML treatment, transformation to AML, and death. An independent data safety monitoring board (DSMB) evaluated safety results to ensure the ongoing safety of patients during the study and to review the interim analysis results (conducted after 50% of the expected deaths had occurred in the study) and sample size assumptions. An extension phase to the protocol allowed eligible patients originally randomized to azacitidine treatment who were still receiving treatment at the end of the study to continue to receive azacitidine (these data not included in this clinical study report). An independent committee of experts in MDS ensured a standardized and validated interpretation of the MDS FAB and World Health Organization (WHO) diagnoses, International Prognostic Scoring System (IPSS) classification, IWG response findings, and response durations.

Number of Patients (Planned and Analyzed): Approximately 354 randomized patients planned; 358 patients randomized and analyzed.

Diagnosis and Main Criteria for Inclusion: 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.

Test Product, Dose and Mode of Administration, Batch Number: Azacitidine vials contained lyophilized azacitidine 100 mg and mannitol 100 mg. These vials were reconstituted with 4 mL sterile water for injection. Azacitidine was injected subcutaneously (SC) at an initial dose of 75 mg/m^2/day for 7 days. The 7-day dosing was repeated every 28 days, with dose adjustment based on predefined hematology and renal laboratory results. Lot numbers of azacitidine used in the study were 406840, 406841, 472204, 716384, and 763281.

Duration of Treatment: Azacitidine treatment was to be continued until the end of the study (investigators were to aim for at least 6 cycles) unless treatment was discontinued due to unacceptable toxicity, relapse after complete or partial response, transformation to AML, or disease progression.

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Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable for BSC only. All comparator study drugs were obtained through the local hospital pharmacy or licensed distributor.

Best supportive care only: BSC could include transfusions, antibiotics, myeloid growth factors (granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor [GM-CSF]) for neutropenic infections. Erythropoietin was not permitted.

Low-dose cytarabine: Low-dose cytarabine SC at an initial dose of 20 mg/m^2/day for 14 days, every 28 to 42 days (optimally for at least 4 cycles). In case of myelotoxicity, the next cycle could be delayed up to 2 weeks; if severe, the duration could be reduced to 7 to 10 days.

Standard chemotherapy: At the induction cycle for standard chemotherapy, intravenous (IV) cytarabine was given at 100 to 200 mg/m^2/day for 7 days, and the preferred anthracycline daunorubicin was given IV at 45 to 60 mg/m^2/day on Days 1, 2, and 3. (Other anthracycline choices included IV idarubicin 9 to 12 mg/m^2/day or IV mitoxantrone 8 to 12 mg/m^2/day.) The first of a maximum of 2 consolidation cycles was to be 28 to 70 days after the start of induction; cytarabine IV was given at 100 to 200 mg/m^2/day for 3 to 7 days, and the same anthracycline that was administered during induction was given IV on Days 1 and 2. The second consolidation cycle was to be 28 to 70 days after the previous cycle.

Criteria for Evaluation:
Efficacy: The primary efficacy endpoint was time to death from any cause. Secondary endpoints were time-to-event analyses (time to transformation to AML or death from any cause, time to transformation to AML, time to disease progression [IWG criteria] or relapse after CR or PR), red blood cell (RBC) and platelet transfusion requirements, rate and duration of hematologic response and improvement, rates of infections, peripheral blood counts, and bone marrow blast counts.

Safety: Safety analyses included adverse events, laboratory measurements, bone marrow aspirates/biopsies (for evaluation of toxicity, if needed), vital signs, and physical examinations.

Statistical Methods: Efficacy Analyses: All efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients. All efficacy analyses used the randomized treatment and not the treatment actually received, if different. The primary efficacy comparison was between azacitidine and the combined CCR groups. Secondary efficacy comparisons of the 3 individual CCR groups were based on the 6 groups of patients defined first by the investigator's selection of the CCR and then, within the investigator's selection of CCR, by the randomized treatment assignment. These comparisons are referred to as within investigator selection comparisons. Time-to-event endpoints (death [overall survival], time to transformation to AML, time to transformation to AML or death from any cause, time to disease progression [IWG criteria] or relapse after CR or PR) were calculated using Kaplan-Meier (KM) survival methods from the date of randomization. Time-to-event endpoints were analyzed using a log rank test stratified by the randomization stratification factors of IPSS classification and FAB classification (per central review). The primary p-value for the primary overall survival (OS) analysis was prespecified to come from the stratified log rank score test. A 2-sided overall alpha of 0.05 was used for the primary endpoint, OS. For the interim analysis of OS, an O'Brien-Fleming type of group sequential monitoring boundary with a Lan-DeMets alpha

spending function was used to preserve the overall alpha level of 0.05. No alpha adjustments were made for secondary endpoints. Time-to-event data were characterized using KM medians with corresponding 95% confidence intervals (CI) and a p value from the stratified log rank test. Hazard ratios and the corresponding 95% CIs were estimated using stratified Cox proportional hazards models.

Time-to-event endpoints (death [OS], time to transformation to AML, and time to transformation to AML or death from any cause) were also performed using the per-protocol population as supportive analyses.

The analyses described above (with the exception of time to disease progression [IWG criteria] or relapse after CR or PR) were also to be conducted individually for azacitidine versus each of the conventional care groups (BSC only, low-dose cytarabine, standard chemotherapy) among patients selected by the investigator to each of those conventional care groups. The primary endpoint was also analyzed using the nonparametric analysis of covariance (ANCOVA) version of the log rank test.

Time to recurrent event analyses were performed using the marginal data models of Anderson-Gill and Wei, Lin and Weissfeld with hazard ratios and corresponding 95% CIs.

Red blood cell and platelet transfusions, peripheral blood counts, infections requiring IV antibiotics, and bone marrow blast counts were summarized descriptively by month and cycle. The number and percentage of patients with each respective category of hematologic response, hematologic improvement, and cytogenetic response were provided. Comparisons of hematologic response, hematologic improvement, and cytogenetic response between azacitidine and the combined CCR group were performed using Fisher's exact test.

An ad hoc analysis of time to transformation to AML during the treatment period was also performed.

Interim Analysis: The protocol called for 1 interim analysis after 83 deaths (50% of the estimated deaths). The database cutoff date for the one (and only) interim analysis was 23 January 2006, the date of the 83rd death.

For the analysis of the primary efficacy variable, time to death from any cause, a comparison between the two treatment groups (azacitidine versus combined CCR) was performed using the stratified log rank test. At the time of the interim analysis, 10% of the alpha (ie, $\alpha = 0.005$, corresponding to an upper boundary of 2.807) was used on the interim analysis, which left $\alpha = 0.048$ available for the final analysis, corresponding to a boundary of 1.977. At the interim analysis, there were 39 and 44 deaths in the azacitidine and combined CCR groups, respectively. The KM median overall survival time was 21 months and 18 months in the azacitidine and combined CCR groups, respectively, a difference of 3 months (stratified log rank $p = 0.43$). As estimated from the corresponding stratified Cox proportional hazards model with treatment as the only term, the azacitidine group had a 15% (95% CI 0.55, 1.32) reduced risk of death compared with patients in the combined CCR group. Additionally, no safety issues were identified. Following the review of the interim analysis data by the DSMB, the DSMB concluded that the study should be continued as planned.

Safety Analyses: All safety analyses were performed on the safety population, defined as all patients who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

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Summary – Conclusions

Study Patients and Conduct: A total of 358 patients (100.0%) were randomized in the study; 179 to the azacitidine treatment group and 179 to combined CCR treatment group. Of the 3 CCR treatment options, BSC (222; 62%) was considered the most appropriate treatment option (prior to randomization) for the majority of patients, followed by low-dose cytarabine (94; 26.3%) and standard chemotherapy (42; 11.7%). Of the 358 patients who were randomized, 340 (95.4%) received at least 1 dose of study drug and 1 postdose safety assessment; these patients comprised the safety population (175 in the azacitidine group, 165 in the combined CCR group). Because the BSC-only treatment may consist of blood products or antibiotics administered only as needed, patients randomized to the CCR group and assigned to BSC only were included in the safety population if they had at least 1 postrandomization assessment.

In azacitidine patients, the most common reason for discontinuing study treatment was progression, which occurred in 12.8% of patients (23 patients), similar to the percentage of patients in the CCR group overall (11.2%, 20 patients). In CCR patients overall, the most common reason for discontinuing treatment was withdrawal of consent for treatment, 20.7% (37 patients), compared with 8.4% of azacitidine patients (15 patients). Note that although patients withdrew consent for treatment, they were still to be followed for survival, including those never treated.

Of the 358 patients randomized, the median age was 69 years (range 38 to 88 years), most patients were Caucasian (98%), and 70% of the patients were male. Forty-eight percent of patients were 65 to 74 years old. The azacitidine and combined CCR treatment groups were comparable for age, gender, race, weight, and body surface area. The azacitidine and combined CCR groups were comparable for comorbidities, including CHF, diabetes, smoking, and time since original MDS diagnosis.

Ninety-five percent of the randomized patients were higher-risk by FAB classification as determined by the Independent review Committee (IRC), with 58% of the patients assessed as RAEB, 34% as RAEB-T, and 3% as modified CMMoL. Eighty-seven percent of randomized patients were assessed by the IRC as IPSS higher-risk; 47% IPSS High and 41% Intermediate-2. Five percent were assessed as Intermediate-1, 8% as indeterminate or not applicable, and none were assessed as Low. Based on the WHO classification as determined by the IRC, 54% of patients were RAEB-2, 32% as AML and 9% as refractory anemia with excess blasts-1 (RAEB-1). The azacitidine and combined CCR groups were comparable for FAB classification, IPSS risk classification, WHO classification, transfusion burden, and hematology parameters.

Efficacy Results: Primary Endpoint: The primary endpoint of this study was time to death from any cause (overall survival). The reverse KM median follow-up time was 21.1 months. The KM median overall survival time was 24.5 months in the azacitidine group compared with 15.0 months in the combined CCR group, an increase in median survival of 9.4 months (stratified log rank $p = 0.0001$) with a corresponding 42% reduced risk of death (95% CI 0.43, 0.77; $p = 0.0002$). The proportion of patients in the azacitidine and combined CCR treatment groups that survived at the 1-year time point was 68.2% and 55.6%, respectively, for a difference of 12.7% (95% CI 2.5, 22.9; $p = 0.0149$). At the 2-year time point, the proportion of patients in the azacitidine group (50.8%) that had survived was approximately 2-fold that of the combined CCR (26.2%) treatment group, for a difference of 24.6% (95% CI 13.1, 36.1; $p < 0.0001$). The KM curves for the azacitidine and combined CCR groups permanently separate at approximately 3.5 months; at this point, 78.2% (140/179) of the azacitidine patients had completed their third cycle of dosing. The overall survival results obtained in the per-protocol (PP) population and subgroups were consistent with those results

obtained in the ITT population, confirming the robustness of the primary efficacy results.

The average number of days dosed per cycle was consistent with the protocol requirements for each regimen. For azacitidine, the average cycle length (median number of days) was 34.0 days, suggesting that investigators were extending the treatment cycle on average by approximately 1 week per the protocol based on the time to nadir and hematological recovery. In the low-dose cytarabine and standard chemotherapy groups, the range of days prescribed in the protocol for each cycle was based on the known toxicity profile of these drugs (28 to 42 days for low-dose cytarabine and 28 to 70 days for standard chemotherapy); the average cycle length was as expected (median of 35.3 days and 71.0 days, respectively) (average cycle length is not applicable for BSC). The median number of treatment cycles in the azacitidine, low-dose cytarabine, and standard chemotherapy groups was 9, 4.5, and 1, respectively.

Secondary Endpoints: As seen with overall survival, the KM median time to death or transformation to AML (whichever occurred first) was significantly longer in the azacitidine group (13.0 months) compared with the combined CCR (7.6 months) group (stratified log rank $p = 0.0025$) with a corresponding 32% (95% CI 0.53, 0.87; $p = 0.0027$) reduced risk of transformation to AML or death.

The KM median time to transformation to AML was greater in the azacitidine group (20.7 months) compared with the combined CCR group (15.4 months); however, the curves were not significantly different (stratified log rank $p = 0.2555$). As estimated from the corresponding stratified Cox proportional hazards model, the azacitidine group had a 17% (95% CI 0.60, 1.15; $p = 0.2562$) reduced risk of transformation to AML compared with patients in the combined CCR group. In an analysis of time to AML during the treatment period, the KM median time was more than 2-fold greater in the azacitidine group (26.1 months) compared with the combined CCR (12.4 months) group (stratified log rank $p = 0.0039$).

Forty-five percent (50/111) of the patients treated with azacitidine who were RBC transfusion dependent at baseline became RBC transfusion independent during the treatment period, compared with 11.4% (13/114) of the patients in the combined CCR group, a statistically significant ($p < 0.0001$) difference of 33.6% (95% CI 22.4, 44.6). The relative risk of RBC transfusions was 0.58 (95% CI 0.54, 0.61; $p < 0.0001$) indicating 42% less risk of RBC transfusion for the azacitidine group relative to the CCR group. In addition, mean hemoglobin concentrations rose to nearly the normal range following azacitidine treatment.

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%; 16/38) and combined CCR groups (40.7%; 11/27). The relative risk of platelet transfusions was 0.64 (95% CI 0.59, 0.71; $p < 0.0001$) indicating 36% less risk of platelet transfusion for the azacitidine group relative to the CCR group. The median duration of platelet transfusion independence was 12.5 months in the azacitidine group and 4.7 months in the combined CCR group, a difference of 7.8 months ($p = 0.0391$). Using an alternative definition of transfusion independence which incorporates criteria of an absolute platelet increase from baseline of 20,000/μL, the percentage of patients who were platelet transfusion dependent at baseline and became platelet transfusion independent was higher in the azacitidine (31.6%) group compared with the combined CCR group (3.7%), a statistically significant ($p = 0.0097$) difference of 27.9% (95% CI 9.3, 45.3).

The overall response rate (CR + PR + stable disease [SD]) as determined by the investigator using IWG 2000 criteria was 70% 126/179) in the azacitidine and 48% (86/179) in the combined CCR group ($p < 0.0001$). Similarly, the overall response (CR + PR) as determined by the investigator was 29% (51/179) in the

azacitidine group and 12% (21/179) in the combined CCR group (p = 0.0001). Complete response was achieved by 17% (30/179) of the azacitidine patients and 8% (14/179) of the combined CCR patients (p = 0.0150).

The overall response rate (CR + PR + SD) as determined by the IRC using IWG 2000 criteria was 91% 163/179) in the azacitidine group compared with 78% (140/179) in the combined CCR group (p = 0.0011). Similarly, the overall response (CR + PR) in the azacitidine group (7%; 12/179) was statistically significantly (p = 0.0113) higher compared with the combined CCR group (1%; 2/179). Complete response was achieved by 4% (7/179) of the azacitidine patients and 1% (2/179) of the combined CCR patients (p = 0.1741). No difference was observed in the median duration of response between the azacitidine and combined CCR groups.

The median time to disease progression, relapse after CR or PR, or death from any cause was prolonged by a median of 5.3 months in the azacitidine group (14.1 months) compared with the combined CCR group (8.8 months)(log rank p = 0.0466).

The percentage of patients in the azacitidine group (49%) with any hematologic improvement was 1.5-fold higher compared with the combined CCR group (29%). Additionally, the median duration of hematologic improvement in the azacitidine group was 8.4 months longer compared with the combined CCR group (log rank p = 0.0002). 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 percentage of patients with a major neutrophil response was similar in the azacitidine (19%) and combined CCR (18%) groups.

The rate of adverse events of infection that required IV antibiotic, antifungal, or antiviral therapy was 1.5 fold higher in the combined CCR group compared with the azacitidine group. The rate of adverse events of infection that required IV antibiotic, antifungal, or antiviral therapy was 0.16 events per patient year in the azacitidine group compared with 0.24 events per patient year in the CCR group. The relative risk of such infections was 0.67 (95% CI 0.35, 1.30; p = 0.1327) indicating 33% less risk of such infections for the azacitidine group relative to the CCR group.

Safety Results: The median duration of treatment in 28-day months was longest for patients in the azacitidine treatment group (10.43 months) compared with for BSC only (6.16 months), low-dose cytarabine (5.71 months), and standard chemotherapy (1.46 months). The total treatment exposure in patient-years to azacitidine and CCR was 169.2 and 90.8, respectively. The total treatment exposure in patient-years to the individual CCR options of BSC only, low-dose cytarabine, and standard chemotherapy was 58.8, 25.5 and 6.5, respectively.

Hematologic treatment-emergent adverse events (TEAEs) were among the events most frequently reported by azacitidine patients; the 2 most frequent events were thrombocytopenia (69.7%) and neutropenia (65.7%), usually Grade 3 or 4. Other hematology events frequently reported included anemia, leukopenia, and febrile neutropenia (anemia and febrile neutropenia were comparable between the azacitidine and BSC-only groups). Of note, however, azacitidine did not increase the risk of events of infection or bleeding when compared with BSC only. In contrast, both standard chemotherapy and low-dose cytarabine were associated with increased risks for both of these events relative to azacitidine. Nonhematologic adverse events

frequently reported in azacitidine patients were events related to either the administration of the drug (injection site reactions, nausea, vomiting) or consequences of the anti-emetic (constipation). These nonhematologic TEAEs (usually Grade 1 or 2) are well recognized events observed with azacitidine treatment and, as such, these events were observed more frequently with azacitidine than with BSC only, even after adjustment for the differences in duration of exposure.

In analyses of the first occurrence of TEAEs by cycle and by cycle onset day, findings showed that in azacitidine patients, most of the frequently reported TEAEs were reported most often during Cycles 1 and 2; and within the cycle, the common hematology events occurred most often during the first 3 weeks of the cycle before decreasing, and events associated with administration of azacitidine occurred most often within the first week of the cycle. These findings suggest a lack of delayed toxicity. In analyses of any occurrence of TEAEs by cycle and by cycle onset day, findings suggested that effects of azacitidine attenuate over time and that there was a lack of cumulative toxicity.

As with pretreatment deaths, the causes of death during the on-treatment and post-treatment periods were consistent with the underlying disease (including infection and hemorrhage) or underlying diseases commonly associated with an older population (including cardiac and respiratory failure). The most common reason for an event to be assessed as serious was hospitalization. Similar to events resulting in death, the most common serious TEAEs resulting in or prolonging hospitalization were events associated with the underlying disease (cytopenias and infection). Overall, a small percentage of patients discontinued study treatment due a TEAE; the most common reason for discontinuation of azacitidine was due to hematological TEAEs in < 5% of patients. No patient discontinued study treatment due to any of the common non-hematological toxicities (ie, nausea/vomiting or injection site reactions). Similarly, TEAEs leading to interruption or reduction of study treatment were primarily hematological events. Most TEAEs were managed with either concomitant medications(s) or transfusions(s).

As seen with the efficacy data, analyses of hematology analytes over time demonstrated that RBC indices, hemoglobin, and platelet values tended to improve over time for patients in the azacitidine groups while the other treatment groups showed little or no changes (hemoglobin and RBC indices) or worsening (platelets) of mean or median values for these analytes. Conversely, patients in the azacitidine group tended to exhibit decreases over time in median ANC and WBC values, which were greater than those noted in the BSC-only group, but smaller than the decreases experienced by patients in the standard chemotherapy group and comparable to the decreases experienced by patients in the low-dose cytarabine group. The decreases in ANC values were not associated with an increased risk for infection in azacitidine treated patients compared to patients treated with BSC only. Analyses of hematology data by National Cancer Institute Common Toxicity Criteria (NCI CTC) grade were consistent with these mean data. Grade 3 or 4 values for hematologic parameters occurred most frequently during the first 2 cycles of azacitidine treatment and tended to decrease in frequency over time.

The median time to nadir values across hematology parameters was 14 to 15 days for the azacitidine group compared with 17 to 21 days for the low-dose cytarabine group and 17 to 23 days for the standard chemotherapy group. The actual nadir values reached by patients in the azacitidine group were comparable to the nadir values experienced by patients in the low-dose cytarabine group and were higher than the nadir values experienced by patients in the standard chemotherapy group.

Laboratory analyses of chemistry data, including electrolytes and measures of hepatic and renal function,

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showed that even after prolonged administration, azacitidine had no potential 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. Other safety data collected during the study were consistent with findings that would be expected in an older population with advanced stages of MDS.

Conclusions: MDS is a serious and life-threatening disease, for which there are currently no available approved therapies that either improve survival or delay transformation to acute myeloid leukemia. While allogeneic hematopoietic stem cell transplantation has the potential for cure, it is only an option for a younger population of MDS patients given the associated treatment-related morbidity and mortality.

In patients with higher-risk MDS, azacitidine treatment resulted in a median overall survival of 24.5 months, a prolongation of 9.4 months over CCR. Additionally, the overall survival results were consistent and robust across all subgroups. Azacitidine is the only agent to prolong survival in higher-risk MDS patients, and therefore influence the natural history of the disease. The time to transformation to AML or death, time to transformation to AML, and time to disease progression and relapse after CR or PR were longer in the azacitidine group than the CCR group. In addition, a reduction in transfusion burden, a reduction in the risk of anemia and thrombocytopenia, and a reduction in the risk of infection was observed with azacitidine compared with CCR. Together, these results suggest that azacitidine has a positive effect on the natural history of the disease. In addition, azacitidine is safe and well tolerated. The safety profile is consistent with the known effects of azacitidine, and these effects can be appropriately managed with routine monitoring.

Based upon these data, azacitidine should be considered first-line therapy for higher-risk MDS patients who are not eligible for curative treatment with allogeneic hematopoietic stem cell transplantation.

Date of the report: 18 December 2007