EISAI INC.

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DACOGEN® (decitabine)

INDICATION: ACUTE MYELOID LEUKEMIA

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ADVISORY COMMITTEE BRIEFING MATERIALS:
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1.0 EXECUTIVE SUMMARY

1.1 Disease Background and Proposed Indication

Adult acute myelogenous leukemia (AML) is a rapidly progressive disease with a median age at onset of 65 to 70 years. Among elderly AML patients (≥ 65 years of age), median survival is typically short (ranging from 3.9 months for patients 65 to 74 years of age to 1.4 months for patients ≥ 85 years of age). Treatment options for elderly AML patients are limited, and outcomes are poor. Elderly patients with AML are more likely than younger patients to have intermediate- or unfavorable-risk cytogenetics, and many may have had an antecedent hematologic disorder. These factors are associated with resistance to chemotherapy and lower complete remission (CR) rates. Moreover, elderly patients with AML are often either not candidates for or choose not to receive standard induction chemotherapy because of poor tolerability and treatment outcomes. Induction chemotherapy is associated with high rates of treatment-related mortality and low CR rates in patients ≥ 65 years of age, and < 10% of patients will survive 2 years. Currently, there are no approved therapies for AML patients who do not receive standard induction chemotherapy. Thus, there is an unmet medical need in this patient population for new agents with established clinical benefit and a favorable safety profile.

Proposed indication: Dacogen is indicated for treatment of AML in adults ≥ 65 years of age who are not considered candidates for induction chemotherapy.

1.2 Clinical Development Program

Dacogen (decitabine) is a nucleoside metabolic inhibitor that was first approved in the United States in May 2006 for the treatment of myelodysplastic syndromes (MDS), and the 5-day dosing regimen used in the AML studies was approved for use in MDS in 2010. Dacogen is believed to exert its antineoplastic effects by causing hypomethylation of DNA and cellular differentiation or apoptosis.

The supplemental New Drug Application (sNDA) is for the treatment of patients with AML. The clinical studies that support the AML sNDA include one randomized, controlled trial (Study 016) and one single-arm supportive study (Study 017) in elderly AML patients. Study 016 was a randomized, open-label, multicenter, global, Phase 3 study that enrolled 485 patients ≥ 65 years of age with newly diagnosed, histologically confirmed, de novo or secondary AML and intermediate- or unfavorable-risk cytogenetics. Study 016 was designed to compare Dacogen (20 mg/m^2 as a 1-hour infusion once daily for 5 consecutive days every 4 weeks) with patient's choice of treatment with the advice of their physician (TC), which included either low-dose cytarabine (20 mg/m^2 subcutaneously once daily for 10 day every 4 weeks) or best supportive care (SC). The primary and secondary efficacy endpoints in Study 016 were overall survival (OS) and the rate of CR + CR with incomplete platelet recovery (CRp).

1.3 Summary of Efficacy

The totality of the clinical evidence from the randomized trial (Study 016) indicates that Dacogen provides a clinically meaningful benefit compared with TC in AML patients ≥ 65 years of age (Table 1). The pre-specified primary analysis showed a 2.7-month improvement in median OS (7.7 months vs 5.0 months) with a hazard ratio of 0.85. However, the stratified, log-rank analysis did not demonstrate statistical significance. Subsequently, an unplanned OS analysis with 1 year of additional follow-up demonstrated the same improvement in median OS with a nominal *p* value of 0.037. The OS advantage achieved with Dacogen was consistently observed across most subgroups. Results from secondary and tertiary endpoints provide additional evidence of the antileukemic effect of Dacogen and support the treatment benefit. Dacogen significantly improved the CR and the CR + CRp rates compared with TC, and produced durable complete remissions. Among patients with a CR, median relapse-free survival was 8.3 months in the Dacogen arm. Dacogen also significantly improved event-free survival (EFS) and progression-free survival (PFS) compared with TC. Finally, the CR rate and median OS observed in Study 016 are supported by data from the single-arm study (Study 017), which demonstrated a 23.6% CR rate (95% CI: 13.2, 37.0) and a median OS of 231 days (7.6 months) in 55 AML patients ≥ 60 years of age with similar disease characteristics who were treated in the United States.

Table 1 Summary of Clinical Efficacy in Study 016, Intent-to-Treat Population

Endpoint	Dacogen (N = 242)	Total TC (N = 243)	Hazard/Odds ratio (95% CI)	*p* value
Median OS, months (95% CI)				
Pre-specified primary analysis (CCO 2009)	7.7 (6.2, 9.2)	5.0 (4.3, 6.3)	0.85 (0.69, 1.04)	0.108
Updated OS analysis (CCO 2010)	7.7 (6.2, 9.2)	5.0 (4.3, 6.3)	0.82 (0.68, 0.99)	0.037[a]
Response rate (independent review), n (%)				
CR + CRp	43 (17.8)	19 (7.8)	2.5 (1.40, 4.78)	0.001
CR	38 (15.7)	18 (7.4)	2.3 (1.25, 4.47)	0.004
Median RFS, months (95% CI)	8.3 (4.6, 11.4)	6.7 (2.9, 13.4)		
Tertiary time to event				
Median EFS, months (95% CI)	3.5 (2.5, 4.1)	2.1 (1.9, 2.8)	0.75 (0.62, .090)	0.003
Median PFS, months (95% CI)	3.7 (2.7, 4.6)	2.1 (1.9, 3.1)	0.75 (0.62, .091)	0.003

Abbreviations: TC = patient's choice of treatment with physician's advice; CI = confidence interval; OS = overall survival; CCO = clinical cutoff; DMT = disease-modifying therapy; CR = morphologic complete remission; CRp = CR with incomplete platelet recovery; RFS = relapse-free survival; EFS = event-free survival; PFS = progression-free survival.

a: Nominal *p* value.

1.4 Summary of Safety

Dacogen was generally well tolerated by patients with AML in studies Study 016 and Study 017 as indicated by the following observations.

- The safety profile was consistent with the known safety profile of Dacogen in patients with MDS,[1] and there were no new safety signals.
- Treatment duration was approximately 2-fold longer in the Dacogen arm (4 versus 2 cycles), suggesting that Dacogen was well tolerated, and the safety profiles of Dacogen and cytarabine were similar.
- As expected, the most prevalent AEs were related to myelosuppression (cytopenias and febrile neutropenia). There was a numerically higher incidence of myelosuppression in the Dacogen arm, but this is unlikely to be clinically significant in the context of AML.
- AEs were generally manageable with standard medical care given by oncologists.
- The rate of discontinuation due to a TEAE was comparable between treatment arms.
- The incidence of 30-day all-cause mortality was low (8%) and similar in both treatment arms.
- There were no clinically meaningful differences in the incidence of infection, bleeding, cardiac AEs, or major central nervous system AEs between treatment arms.

1.5 Benefit-Risk Summary

Treatment options for elderly patients with AML are limited, and outcomes are poor. Elderly patients with AML are often either not candidates for or choose not to receive standard induction chemotherapy because of poor tolerability and treatment outcomes. Currently, there are no approved therapies for AML patients who do not receive standard induction chemotherapy.

Data from the randomized, Phase 3 trial (Study 016) demonstrate that Dacogen is more effective than low-dose cytarabine or SC in this patient population. In addition to the primary OS analysis that showed a clinically meaningful trend for improvement in survival favoring Dacogen, an updated OS analysis with 1 year of additional follow-up supports the conclusion that the OS difference observed in the primary analysis represents a real treatment effect. Moreover, Dacogen significantly improved the rate of CR and CR + CRp, EFS, and PFS compared with TC. Taken together, these data provide evidence of a clinically meaningful treatment effect and support the clinical benefit of Dacogen in this setting. Dacogen also demonstrated an acceptable safety profile that is consistent with the known safety profile of Dacogen in patients with MDS and comparable to low-dose cytarabine in elderly patients with AML.

1.6 Overall Conclusion

There is an unmet need for new therapeutic options in this patient population. The totality of the efficacy and safety data indicate that Dacogen has a favorable benefit-risk profile in AML patients ≥ 65 years of age who do not receive induction chemotherapy.

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition and Notes
AE	Adverse event
AHD	Antecedent hematologic disease
AML	Acute myelomatous leukemia
ANC	Absolute neutrophil count
AUC	Area under the concentration-time curve
CI	Confidence interval
C_{max}	Maximum observed concentration
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
CR	Complete remission
CRc	Cytogenetic complete remission
CRi	Morphologic complete remission with incomplete blood count recovery
CRp	Morphologic complete remission with incomplete platelet recovery
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DMSO	Dimethylsulfoxide
DMT	Disease-modifying therapy
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
FAB	French-American-British (subtypes)
FDA	Food and Drug Administration
IRC	Independent Review Committee
ITT	Intent to treat
i.v.	Intravenous
IWG	International Working Group
LINE	Long interspersed element
LDAC	Low-dose cytarabine
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable, or not available
NDA	New drug application
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per-protocol (population)
PR	Partial remission
QoL	Quality of life
RFS	Relapse-free survival
SAE	Serious adverse event
SC	Supportive care
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
sNDA	supplemental New Drug Application
SPA	Special Protocol Assessment

Abbreviation	Definition and Notes
SWOG	Southwest Oncology Group
TC	Patient's choice of treatment with the advice of their physician
TEAE	Treatment-emergent adverse event

2.0 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Overview of Acute Myeloid Leukemia and Unmet Need in Elderly Patients

Acute myelogenous leukemia (AML) is a rapidly progressive disease, and median survival among patients ≥ 65 years of age is typically short. An analysis of the linked SEER-Medicare database indicated a median overall survival (OS) of 2.4 months across all patients ≥ 65 years of age (N = 3,439), which ranged from 3.9 months for patients 65 to 74 years of age to 1.4 months for patients ≥ 85 years of age.[2] Unfortunately, this applies to approximately half of adult patients with AML; median age at onset is 65 to 70 years.[3] Treatment options for elderly AML patients (≥ 65 years of age) are limited, and outcomes are poor.[4] The reasons for poor clinical outcomes in elderly AML patients are complex. Elderly patients with AML are more likely than younger patients to have intermediate- or unfavorable-risk cytogenetics, and many have secondary AML. These factors are associated with resistance to chemotherapy and low complete remission (CR) rates.[5] Moreover, elderly patients with AML are often not good candidates for standard induction chemotherapy because of poor tolerability and treatment outcomes.[2,6-8] Compared with younger patients, treatment-related mortality rates are high, and CR rates are low, resulting in poor survival outcomes. Currently, there are no approved therapies for AML patients who do not receive standard induction chemotherapy. There has been no improvement in therapy for these patients in several decades, and no new treatments have been approved for AML in the United States since Mylotarg® was approved in 2000, and that drug has subsequently been withdrawn from the market. Thus, there is an unmet medical need for new agents with established clinical benefit and an acceptable safety profile in elderly AML patients.

2.2 Limitations of Current Treatment Options for Elderly AML Patients

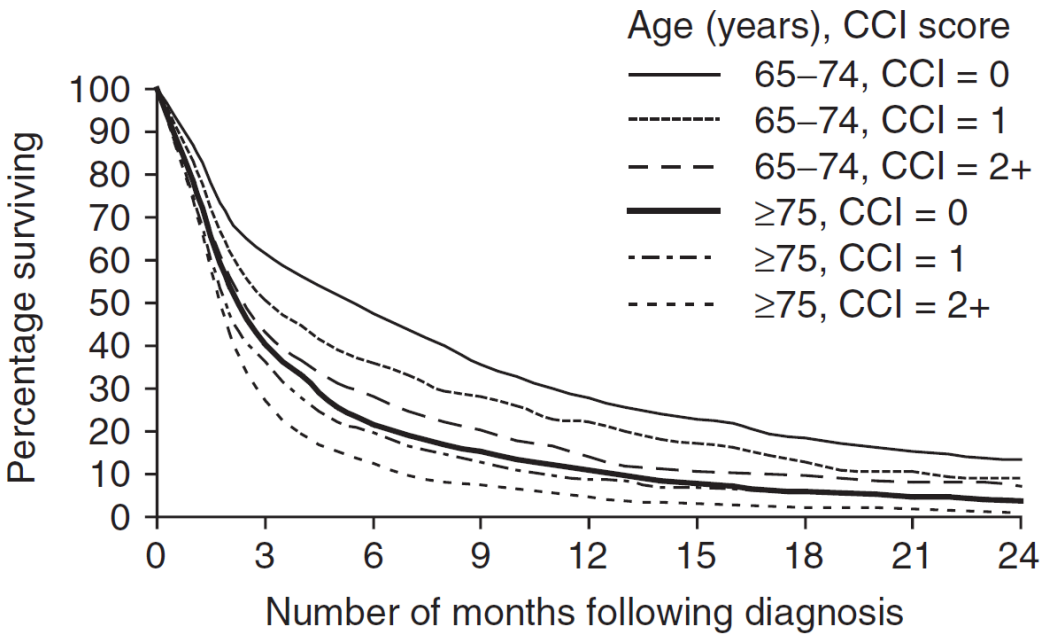
Treatment options for elderly patients with AML include standard induction chemotherapy (for a subset of patients who are fit enough to tolerate it and desire aggressive therapy), low-dose cytarabine (LDAC), investigational therapy, or supportive care (SC). The Medicare data indicate that the majority of elderly AML patients are not treated aggressively and are often referred to hospice for SC, or they may be enrolled in a clinical trial of an investigational agent. In the United States, these patients may receive a hypomethylating agent such as Dacogen or 5-azacitidine, both of which are approved for the treatment of myelodysplastic syndromes (MDS) and have demonstrated activity in AML.[9-12] Treatment with LDAC is an accepted standard of care for elderly AML patients who are not candidates for or choose not to receive standard induction chemotherapy.[4] The data supporting the use of LDAC in this setting come from a subset analysis of the AML14 trial showing significant improvements in CR rate and overall survival (OS) compared with hydroxyurea.[13] Although LDAC was fairly well tolerated and demonstrated a treatment advantage compared with hydroxyurea in this study, it is not approved for this patient population.

Unfortunately, the few available treatment options for elderly AML patients have major limitations. Induction chemotherapy is associated with high rates of treatment-related mortality (20% to 30%) and low CR rates (30% to 50%) in patients ≥ 65 years of age, and < 20% of patients will survive 2 years.[14] In the AML14 trial, patients ≥ 65 years of age (n = 217) who

received LDAC had an 18% CR rate, and median OS was approximately 4 months.[13] Because of these poor outcomes and the potential for life-threatening toxicity, less than 35% of elderly AML patients in the United States receive any chemotherapy.[2,7] With regard to investigational agents for the treatment of elderly patients with AML, there has been a string of recent failures, including tipifarnib, clofarabine, laromustine, gemtuzumab ozogamicin, and lintuzumab.

In contrast to younger adults with AML for whom intensive chemotherapy with or without stem cell transplantation results in long-term survival for approximately 30% of patients, very few patients ≥ 65 years of age will survive more than 2 years from diagnosis.[15,16] In the CALGB 8461 study, 5-year survival rates among patients treated with intensive chemotherapy were 8% for patients age 60 to 69 years, 5.2% for patients age 70 to 79 years, and 0% for patients > 80 years of age.[17] Lang et al[2] reported OS by age and Charlson Comorbidity Index (CCI) based on an analysis of 3439 patients in the Medicare database with an initial diagnosis of AML between 1991 and 1999 (Figure 1). This represents real-world outcomes in an unselected population of elderly AML patients, of whom 34% received induction chemotherapy. This study reported a median OS of 2.4 months and a 2-year survival rate of only 7% for patients ≥ 65 years of age.

Figure 1 Overall Survival by Age Cohort and Charlson Comorbidity Index



Reproduced with permission from Lang et al.[2]

Given these poor clinical outcomes, treatment decisions in elderly patients with AML are difficult. Aggressive treatment necessitates hospitalization and separation from family, has toxic and potentially fatal side effects, and is often ineffective. There are several factors that influence the treatment decision. The wishes of the patient and their family, performance status, comorbidities, and other age-related health and social factors must be considered.

In addition to age and comorbidities, cytogenetics are also important for defining prognostic subgroups in AML. Cytogenetic risk groups defined according to Southwest Oncology Group (SWOG) criteria are favorable, intermediate, or unfavorable. These risk groups predict the probability that a patient will achieve a CR when treated with induction chemotherapy and correlate with their survival prognosis.[18] Patients with unfavorable cytogenetics have significantly lower CR rates and shorter survival compared to patients with favorable cytogenetics. An analysis of cytogenetics in 635 elderly AML patients (≥ 60 years of age) showed that complex karyotypes (≥ 5 abnormalities) were common in this population and were associated with the worst prognosis.[17] In addition, secondary AML due to an antecedent hematologic disorder (AHD) is more resistant to chemotherapy, and those patients are less likely to achieve a CR or have prolonged survival. Therefore, elderly patients, who often have intermediate- or unfavorable-risk cytogenetics and secondary AML, typically have a poor prognosis and may incur greater risk and less benefit from standard induction chemotherapy.

2.3 Rationale for Development of Dacogen

For the reasons cited above, there is a clear unmet medical need for additional effective treatment options in elderly patients with AML for whom standard induction chemotherapy is often not used. In this setting, LDAC can be used, and it has been shown to improve OS in a randomized trial compared with hydroxyurea.[13]

Hypomethylating agents represent a rational approach to the treatment of AML. Aberrant DNA methylation has been reported to be the most frequent molecular alteration in AML.[19] Many genes are frequently methylated in AML including p15, estrogen receptor, calcitonin, and ID-4, among others.[20-22] Christiansen et al also showed that methylation of p15 predicts poor prognosis in AML.[21] In addition, Rush et al identified epigenetic changes that appear unique to AML and have apparent preferential methylation on chromosome 11.[23] Recently, Suzuki et al showed that DKK1 methylation is a risk factor for poorer overall prognosis in AML.[24]

Dacogen has demonstrated clinical benefit in the treatment of patients with MDS, and is thought to work via epigenetic modulation rather than by traditional cytotoxic activity. It is believed to have antineoplastic effects as a result of hypomethylation of DNA, which induces cellular differentiation or apoptosis. Epigenetic gene silencing induced by DNA methylation can be reversed via pharmacologic inhibition of DNA methyltransferases with agents such as Dacogen. The end result may be the induction of differentiation as well as activation of tumor suppressor genes, both of which have implications for the treatment of AML.

Phase 1 and Phase 2 studies of Dacogen in elderly patients with AML have investigated several different dosing regimens and have demonstrated that Dacogen has promising antileukemic activity in this setting.[9-11] Based on the results of a multicenter Phase 2 study using the standard 5-day regimen in patients ≥ 60 years of age,[11] the National Comprehensive Cancer Network (NCCN) guidelines have included Dacogen as an option for low-intensity therapy in AML. More recently, another large Phase 2 study conducted at the Ohio State University investigated a 10-day regimen in 53 patients with a median age of 74 years and demonstrated a response rate of 47% with a median OS of approximately 1 year.[9]

3.0 PRODUCT OVERVIEW

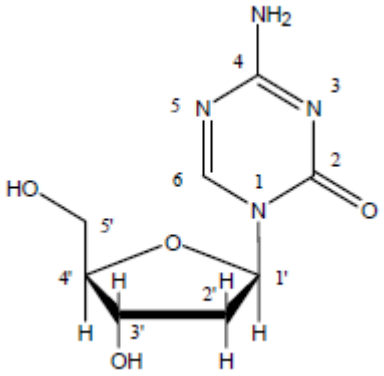
Dacogen® (decitabine) is a nucleoside metabolic inhibitor that was first approved in the United States (US) in May 2006 for the treatment of MDS, including previously treated and untreated, de novo and secondary MDS of all French-American-British (FAB) subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.[1]

3.1 Physical and Chemical Characteristics

Dacogen contains decitabine (5-aza-2'deoxycitidine), an analogue of the natural nucleoside 2'-deoxycytidine. Dacogen is a fine, white to almost white powder with the molecular formula of $C_8H_{12}N_4O_4$ and a molecular weight of 228.21. The chemical name is 4-amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin2(1H)-one. Figure 2 provides the structural formula for Dacogen.

Each 20 mL, single dose, glass vial contains 50 mg Dacogen, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide. Dacogen is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; Dacogen is sparingly soluble in water and soluble in dimethylsulfoxide (DMSO).

Figure 2 Chemical Structure



3.2 Mechanism of Action

At the doses used in the clinical studies, Dacogen is believed to exert its antineoplastic effects by causing hypomethylation of DNA and cellular differentiation or apoptosis. Dacogen inhibits DNA methylation *in vitro* at concentrations that do not cause major suppression of DNA synthesis. Dacogen-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of Dacogen may also be attributed to the formation of covalent adducts between DNA methyltransferase and Dacogen incorporated into DNA. Non-

proliferating cells are relatively insensitive to Dacogen. In human leukemic cell lines, inhibition of DNA methylation, induction of cellular differentiation, and antiproliferative effects were observed at concentrations of 0.5 μM to 1 μM.[25-27]

3.3 Clinical Pharmacology

The pharmacokinetics (PK) of Dacogen has been previously studied in both MDS and AML patients. A population PK model was developed and used to assess Dacogen plasma concentration data from 23 patients enrolled in Study 016. The population PK parameter estimates for a typical 70-kg patient based on a total of 59 patients receiving Dacogen at a dose of 20 mg/m^2 as a 1-hour intravenous (i.v.) infusion for 5 consecutive days in 28-day (4-week) cycles are presented in Table 2.

Table 2 Population Pharmacokinetic Parameter Estimates

Pharmacokinetic Parameter	Estimate	Bootstrap 95% CI
C_{max} (ng/mL)	107	88.5 - 129
$AUC_{0-\infty}$ (ng•h/mL)	116	96.4 - 139
$T_{½}$ (h)	1.14	0.90 - 1.33
CL (L/h/m^2)	172	144 - 208
VDss (L)	116	84.1 - 153

Abbreviations: CI, confidence interval, C_{max}, maximum concentration; AUC, area under the concentration-time curve; $T_{½}$, time to half maximum concentration; CL, clearance; VDss volume of distribution at steady state.
Source: Pop PK report.

Sex, weight, body surface area, body mass index, total bilirubin concentration, and calculated creatinine clearance were covariates in the analysis. Given the small amount of data, covariate modeling aimed to detect strong trends rather than obtain precise estimates of the covariate effects. No influential covariates were identified, except sex, which yielded results similar to the observations provided in earlier population PK analyses. Clearance for females was 12.1% (95% confidence interval [CI]: 0.5, 25.6%) lower than for males. The effect was considered small relative to the inter-individual variability (coefficient of variance = 55.7%) and not clinically relevant. Analyses suggested that the volume of distribution was proportional to body weight and clearance was proportional to body surface area. Thus, dosing by body surface area provides equal exposures (area under the concentration-time curve) for patients of different body sizes.

4.0 CLINICAL DEVELOPMENT PROGRAM

Dacogen was first approved in the United States on May 02, 2006, for treatment of patients with MDS. Approval was based on efficacy and safety results from one randomized open-label, multicenter, controlled trial evaluating 170 adult patients with MDS and three open-label, single-arm, multicenter studies. The regimen used in this initial approval was 15 mg/m^2 three times daily for 3 days of every 6-week cycle. All trials demonstrated consistent overall response rates (complete remission [CR] + partial remission [PR]). Subsequently, in 2010, a 5-day outpatient regimen (identical to the regimen used in the AML studies) was approved for the treatment of MDS.

4.1 Overview of Clinical Development Program in AML

The clinical studies that support the AML indication include one randomized, controlled trial (Study 016) and one smaller single-arm supportive study (Study 017) in elderly AML patients (Table 3).

Table 3 Clinical Development Program in AML

Study #	Study Design	Regimens	Primary Endpoint	Patients Enrolled
016	Open-label, multicenter, randomized, 2-arm, controlled Phase 3 study	**Arm A**: Dacogen 20 mg/m^2 1-hr i.v. infusion daily x 5 day every 4 weeks **Arm B**: Patient choice of cytarabine 20 mg/m^2 subcutaneously once daily for 10 day every 4 weeks or supportive care	Overall survival measured from date of randomization to date of death	485
017[11]	Open-label, multicenter, nonrandomized, single-arm, uncontrolled Phase 2 study	Dacogen 20 mg/m^2 1-hr i.v. infusion daily x 5 d every 4 weeks	Rate of morphologic CR in the ITT population, as determined from the expert assessments of responses based on IWG 2003 criteria	55

Abbreviations: CR = complete remission; ITT = intent to treat.
Source: Investigator brochure; Cashen AF, et al. *J Clin Oncol.* 2010;28(4):556-561.[11]

4.1.1 Study 016

Study 016 was a randomized, open-label, multicenter, global, Phase 3 study in patients ≥ 65 years of age with newly diagnosed, histologically confirmed, de novo or secondary AML and intermediate- or unfavorable-risk cytogenetics (defined by SWOG criteria). Study 016 was designed to compare Dacogen with treatment choice (TC), which included either low-dose cytarabine or SC. The primary and secondary efficacy endpoints were OS and the rate of morphologic CR + complete remission with incomplete platelet recovery (CRp) in the intent-to-treat (ITT) population. Study 016 was designed and initiated based on academic studies

demonstrating that Dacogen has antileukemic activity and induces durable CRs in patients with AML.[10,28-31] As described above, there is a strong scientific rationale for investigating hypomethylating agents in AML as well as in MDS, for which Dacogen is approved.

4.1.2 Study 017

Study 017 was an open-label, single-arm, multicenter, Phase 2 trial of first-line Dacogen treatment in elderly patients (age ≥ 60 years) with de novo or secondary AML and intermediate- or unfavorable-risk cytogenetics, and it was conducted entirely in the United States. The patient population enrolled in Study 017 was very similar to the population enrolled in Study 016. Eligible patients were not candidates for standard induction chemotherapy, bone marrow or stem cell transplant, treatment with Mylotarg® (gemtuzumab ozogamicin; Wyeth), or treatment with transretinoic acid. The primary endpoint was the rate of morphologic CR in the ITT population.

4.2 Rationale for Dose Selection and Treatment Duration

The dosing regimen for Study 016 and Study 017 was 20 mg/m^2 Dacogen given as a 1-hour i.v. infusion once daily for 5 consecutive days every 4 weeks. This regimen was in clinical use for the treatment of MDS at the time Study 016 was initiated and was subsequently approved for use in MDS.

Support for the Dacogen dosing regimen for the treatment of elderly AML patients is based on pharmacokinetic and pharmacodynamic data and in vitro and cellular hypomethylation studies. In human leukemic cell lines, inhibition of DNA methylation and induction of cellular differentiation reach a plateau, or even decrease above concentrations of 0.5 μM to 1 μM.[25-27] Pharmacokinetic analyses from Study 017 and Study 020 demonstrated a maximum observed concentration (C_{max}) of 137 and 147 ng/mL (0.6 and 0.64μM), respectively. These findings were similar to those predicted using a population PK model that included PK data from patients with AML and MDS from studies Study 016, Study 017, and Study 020. The model predicted a C_{max} of 107 ng/mL (95% CI: 88.5, 129 ng/ml) or 0.47 μM (95% CI: 0.39, 0.57 μM). These C_{max} concentrations are above the in vitro hypomethylating concentration of Dacogen.

In clinical samples, Dacogen induces a dose-dependent linear decrease in methylation of Alu and long interspersed element (LINE) sequences at doses of 5 to 20 mg/m^2 per day ($r^2 = 0.88$; $p = 0.046$) with no significant increase in hypomethylation above 20 mg/m^2.[31] The plateau effect in hypomethylation seen in clinical samples mirrors that observed in nonclinical studies in leukemic cell lines.

Using a LINE1 assay as a surrogate measure of global DNA methylation,[29] hypomethylation was evaluated in MDS and chronic myelomonocytic leukemia (CMML) patients receiving 3 different Dacogen regimens: 20 mg/m^2 i.v. for 5 days; 20 mg/m^2 subcutaneously for 5 days; or 10 mg/m^2 i.v. for 10 days. The dosing regimen of 20 mg/m^2 i.v. for 5 days was superior to the other regimens tested in terms of complete remission rates and induction of hypomethylation of LINE sequences.

4.3 Interactions With FDA

Dacogen was first approved in the United States on May 02, 2006, for treatment of patients with MDS. The 5-day dosing regimen used in the AML trials was approved for treatment of MDS on March 11, 2010. Orphan drug designation for the AML indication was granted in May 2006.

Study 016 was designed and conducted in accordance with Division feedback via the Special Protocol Assessment (SPA) process. Several written communications regarding protocol design and conduct were exchanged between February 2005 and August 2005 and Agency feedback was incorporated into the design of Study 016. In addition, there was a pre-sNDA teleconference on February 22, 2010, during which an agreement on content and format of the proposed AML sNDA was reached. The sNDA for AML was submitted on May 6, 2011.

4.4 Proposed Indication

Dacogen is proposed for the treatment of AML in adults ≥ 65 years of age who are not considered candidates for induction chemotherapy.

5.0 SUMMARY OF CLINICAL EFFICACY IN STUDY 016

5.1 Study Design

This was a randomized, open-label, multicenter, global, Phase 3 study in patients ≥ 65 years of age with newly diagnosed, histologically confirmed, de novo or secondary AML and intermediate- or unfavorable-risk cytogenetics. This study compared Dacogen treatment with the patient's choice of treatment (with physician's advice), which included either low-dose cytarabine or best supportive care (SC). Patients with any FAB AML subtype except acute promyelocytic leukemia (M3 classification) were eligible for the study.

Before randomization, patients were asked to select their choice of therapy (cytarabine or SC) in the event that they were randomized to the TC arm. Patients were stratified before randomization based on age (65 to 69 years vs 70+ years), Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0 to 1 vs 2), and cytogenetic risk status (intermediate or unfavorable) following the published SWOG criteria.[18] A total of 485 patients were randomly assigned to treatment using an interactive voice response system. Because AML is an orphan indication with an estimated 13,000 new cases annually in the US, of which approximately half occur in elderly patients (age 65 or older), it was necessary to conduct a global study to accrue the required number of patients. Enrollment began in January 2006, and the last patient was enrolled in April 2009.

Eligible patients were randomly allocated in a 1:1 ratio to one of two treatment arms:

- **Arm A**: treatment choice (TC) of either SC or 20 mg/m^2 cytarabine given subcutaneously once daily for 10 consecutive days, repeated every 4 weeks. A total of 243 patients were randomly assigned to this arm.
- **Arm B**: 20 mg/m^2 Dacogen given as a 1-hour i.v. infusion once daily for 5 consecutive days every 4 weeks. A total of 242 patients were randomly assigned to this arm.

Supportive care for this study was defined as treatment given with the intent to maximize quality of life rather than to achieve a specific antileukemic effect. Supportive care specifically excluded surgery, immunotherapy, biologic therapy, radiotherapy (with the exception of palliative radiotherapy), anticancer hormonal therapy, and oral or systemic chemotherapy in which the goal was to either eradicate or slow the progression of the disease. Those therapies considered acceptable included, but were not limited to, treatment with antibiotics and antifungal agents, packed red blood cells or whole blood transfusions, fresh frozen plasma, platelet transfusions, nutritional support (enteral or parenteral), and focal external beam radiation given for symptomatic control of pain. Patients were allowed to receive erythropoietin and darbepoetin during this study; however, use of granulocyte-colony stimulating factor and granulocyte macrophage-colony stimulating factor was restricted to the treatment of severe infection.

Patients could continue study treatment until disease relapse or progression, they were no longer receiving clinical benefit from therapy (Dacogen- and cytarabine-treated patients), death, unacceptable toxicity or an intercurrent illness that prevented further administration of treatment, the patient or physician requested discontinuation, or changes in the patient's

condition rendered the patient unacceptable for further treatment in the judgment of the investigator.

5.1.1 Statistical Analysis

The protocol-specified primary analysis of OS was planned when 385 death events had occurred. The study was designed to detect a 25% reduction in mortality risk (median survival times were assumed to be 8 months for the Dacogen arm and 6 months for the TC arm) with at least 80% power while maintaining an overall type I error of 0.05 (2-sided). After adjusting for two planned interim analyses, the remaining significance level for the final analysis was 0.0462. In addition, an unplanned updated OS analysis was performed using a cutoff date 1 year after the original data cutoff date. Sensitivity analyses were performed to further evaluate the OS results and included: 1) an analysis of OS in the per protocol (PP) population; 2) an analysis of OS censoring patients at the time they received subsequent disease-modifying therapy (DMT); and 3) an analysis of OS excluding patients who received a hypomethylating agent as subsequent therapy.

5.1.2 Interim Analyses

Two interim analyses were planned and performed after approximately one-third and two-thirds of the 385 deaths had occurred with the Lan-Demets alpha spending function of the O'Brien-Fleming type. The results of these two interim analyses were reviewed at the closed Data Monitoring Committee (DMC) meetings of April 10, 2008, and December 17, 2008. Predefined stopping criteria were not met, and the DMC recommended that the study continue on both occasions. The committee also reviewed the study data five other times for the purpose of safety monitoring.

5.1.3 Independent Review Committee (IRC)

An IRC consisting of 2 clinical leukemia experts reviewed all data pertinent to assessment of morphologic response and disease progression. These clinical experts were board-certified hematologists with experience in the management of AML, and they were independent of the Sponsor and blinded to treatment assignment. Bone marrow smears provided by the study sites were reviewed centrally by a single, independent, study-blinded hematopathologist under light microscopy, and the results for each patient were documented in a report. The bone marrow results and additional clinical data were then independently evaluated by the IRC in a blinded fashion, and a disease response status was assigned.

The criteria for determining disease response and progression followed the criteria established by the International Working Group (IWG) in 2003.[32] The criteria applied in Study 016 are summarized in Table 4 below.

Table 4 Definitions for Response and Progression

	Definition
Morphologic complete remission (CR)	Morphologic leukemia-free state defined as < 5% blasts in an aspirate sample with marrow spicules and a count of ≥ 200 nucleated cells (there should have been no blasts with Auer rods or persistence of extramedullary disease) plus absolute neutrophil count (ANC) > 1,000/µL, platelet count of ≥ 100,000/µL, and the patient must have been independent of transfusions for at least 1 week before each assessment. There was no duration requirement for confirmation of this designation.
Morphologic complete remission with incomplete platelet recovery (CRp)	Morphologic CR without the requirement of platelet count ≥ 100,000/µL.
Morphologic complete remission with incomplete blood count recovery (CRi)	Morphologic CR with residual neutropenia (< 1,000/µL) or thrombocytopenia (< 100,000/µL).
Cytogenetic complete remission (CRc)	Morphologic CR plus a reversion to a normal karyotype. For this study, reversion of an abnormal karyotype to a normal karyotype was defined as no clonal abnormalities detected in a minimum of 20 mitotic cells.
Disease progression (PD)	<u>During the first cycle</u>: Based on peripheral blood counts, evidence of new extramedullary disease and/or the clinical judgment of the investigator. – If a bone marrow (BM) assessment was NOT performed, then a > 50% increase in peripheral blast count was considered PD. – If a bone marrow assessment was performed in the first cycle or before the start of the second cycle, then a > 25% increase from baseline blast count on BM aspirate was considered PD. <u>During subsequent cycles</u>: – A > 50% increase from baseline in peripheral or BM blast count, clinical evidence of new extramedullary disease, or the clinical judgement of the investigator. <u>In patients with PR or stable disease</u>: Based on BM or peripheral blast count, evidence of new extramedullary disease, and/or the clinical judgement of the independent expert reviewers. – If a BM assessment was NOT performed, a > 50% increase in peripheral blast count over nadir. – If a BM assessment was performed, a > 25% increase in BM blast count over nadir.
Relapse from CR	Reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the BM not attributable to any other cause (e.g., bone marrow regeneration after consolidated therapy). The appearance of new dysplastic changes or the reappearance or development of cytologically proven extramedullary disease.

Source: Study 16 CSR Table 5.

5.1.4 Efficacy Endpoints

The pre-specified primary efficacy endpoint was OS using the original data cutoff date of 28 October 2009 after 385 deaths were reported. This was the only endpoint controlled for type I error.

The secondary efficacy endpoint was the proportion of patients achieving CR + CRp (based on IWG 2003 criteria) as determined by the IRC.

Tertiary efficacy endpoints specified in the study protocol included cytogenetic CR (for patients with abnormal karyotype at baseline), event-free survival (EFS), relapse-free survival (RFS), patient-reported quality of life (QoL) based on EORTC QLQ-C30, and Dacogen population pharmacokinetics.

The analysis populations included the ITT, per-protocol (PP), and safety populations (Table 5).

- **Intent-to-Treat:** all patients randomly allocated to a treatment arm. This was the primary population for all efficacy analyses.
- **Per-Protocol:** all patients randomly allocated to a treatment arm and who received at least two cycles of treatment (included supportive care patients who had a Cycle 2 visit). Patients who died or discontinued for progressive disease before receiving 2 cycles were included in the PP population. Patients who achieved a CR and discontinued for a bone marrow transplant were also included. Patients with major protocol deviations were excluded from the PP population, in accordance with the statistical analysis plan.
- **Safety:** all randomized patients who received at least 1 dose of study drug (Dacogen or cytarabine) and patients who received SC only.

Table 5 Analysis Populations for Study 016

	Patients, n (%)			
		Treatment Choice		
Population	**Dacogen (N = 242)**	**Total TC (N = 243)**	**Cytarabine (N = 215)**	**SC (N = 28)**
ITT	242 (100.0)	243 (100.0)	215 (100.0)	28 (100.0)
Per-protocol	203 (83.9)	193 (79.4)	177 (82.3)	16 (57.1)
Safety	238 (98.3)	237 (97.5)	209 (97.2)	28 (100.0)

Abbreviations: TC = patient's choice of treatment with physician's advice; SC = supportive care.
Source: Study 016 CSR, Table 1, p 3, Appendix 16.1.9.1

5.2 Demographics and Baseline Disease Characteristics

Patient demographic and baseline disease characteristics were generally well balanced between treatment arms (Table 6 and Table 7). Median age was 73 years (range 64 to 91 years), and approximately 40% of patients in both arms were age 75 year or older. The majority of patients had an ECOG PS of 1 or 2.

Table 6 Baseline Demographic Characteristics (Study 016)

Characteristic	Dacogen (N = 242)	Total TC (N = 243)
Median Age, years (range)	73 (64 - 89)	73 (64 - 91)
Age category, n (%)		
< 65 years	3 (1.2)	1 (0.4)
65 - 69 years	68 (28.1)	69 (28.4)
70 - 74 years	76 (31.4)	74 (30.5)
75 - 79 years	65 (26.9)	57 (23.5)
≥ 80 years	30 (12.4)	42 (17.3)
Sex, n (%)		
Male	137 (56.6)	151 (62.1)
Female	105 (43.4)	92 (37.9)
ECOG PS, n (%)		
0	42 (17.4)	47 (19.3)
1	140 (57.9)	131 (53.9)
2	60 (24.8)	65 (26.7)

Abbreviations: TC = patient's choice of treatment with physician's advice; ECOG PS = Eastern Cooperative Oncology Group performance status.
Source: Study 16 CSR pages 75 and 76

Baseline disease characteristics were representative of the general population of elderly patients with AML (Table 7). Importantly, more than one-third of patients in both arms had unfavorable-risk cytogenetics. Although the proportion of patients with secondary AML was balanced across arms, an imbalance was observed in the percentage of patients with certain types of secondary AML. Among those with secondary AML, a higher proportion of patients in the Dacogen arm had a prior myeloproliferative disorder (18.4%) than in the TC arm (9.5%), and more patients in the Dacogen arm had prior leukemogenic exposure (13.8%) than in the TC arm (2.4%).

Table 7 Baseline Disease Characteristics (Study 016)

Characteristic	Dacogen (N = 242)	Total TC (N = 243)
Type of AML, n (%)		
de novo	155 (64.0)	157 (64.6)
Secondary	87 (36.0)	84 (34.6)
N/A	0	2 (0.8)
Type of secondary AML, n (%)	**(n = 87)**	**(n = 84)**
MDS	59 (67.8)	74 (88.1)
Myeloproliferative disorder	16 (18.4)	8 (9.5)
Proven leukemogenic exposure	12 (13.8)	2 (2.4)
Median WBC count (range), $10^3/\mu L$	3.1 (0.3 – 127.0)	3.7 (0.5 – 80.9)
Median blast counts in marrow (range), %	46.6 (3 – 100)	45.0 (0 – 100)
Blasts in bone marrow – category, n (%)	(n = 241)	(n = 241)
< 20	4 (1.7)	8 (3.3)
20 - 30	65 (27.0)	58 (24.1)
31 - 50	67 (27.8)	74 (30.7)
> 50	105 (43.6)	101 (41.9)
Cytogenetic classification of risk, n (%)	**(n = 241)**	**(n = 242)**
Intermediate	152 (63.1)	154 (63.6)
Unfavorable	87 (36.1)	87 (36.0)
N/A	2 (0.8)	0
Unknown	0	1 (0.4)

Abbreviations: AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; N/A = not available; SD = standard deviation; TC = patient's choice of treatment with physician's advice; WBC = white blood cell.
Source: Study 016 CSR pgs 77-81.

5.3 Patient Disposition

Table 8 summarizes the reasons for treatment discontinuation at the 28 October 2009 data cutoff date. There was no limit to the number of cycles that patients could receive, and there was no category for "Completed study."

Table 8 Patient Disposition (Study 016)

	Patients, n (%) Treatment Choice			
	Dacogen (N = 242)	**Total TC (N = 243)**	**Cytarabine (N = 215)**	**SC (N = 28)**
Discontinued	211 (87.2)	228 (93.8)	200 (93.0)	28 (100.0)
Ongoing at database lock	31 (12.8)	15 (6.2)	15 (7.0)	0
Reason for discontinuation of treatment				
Progressive disease	96 (39.7)	116 (47.7)	112 (52.1)	4 (14.3)
Adverse event	19 (7.9)	26 (10.7)	25 (11.6)	1 (3.6)
Patient decision	17 (7.0)	15 (6.2)	5 (2.3)	10 (35.7)
Non-compliance	1 (0.4)	3 (1.2)	1 (0.5)	2 (7.1)
Death	62 (25.6)	43 (17.7)	35 (16.3)	8 (28.6)
Investigator decision	9 (3.7)	15 (6.2)	15 (7.0)	0
Other	7 (2.9)	10 (4.1)	7 (3.3)	3 (10.7)

Abbreviations: SC = supportive care; TC = patient's choice of treatment with the advice of their physician.
Source: Study 016 CSR p 74.

5.4 Efficacy Results

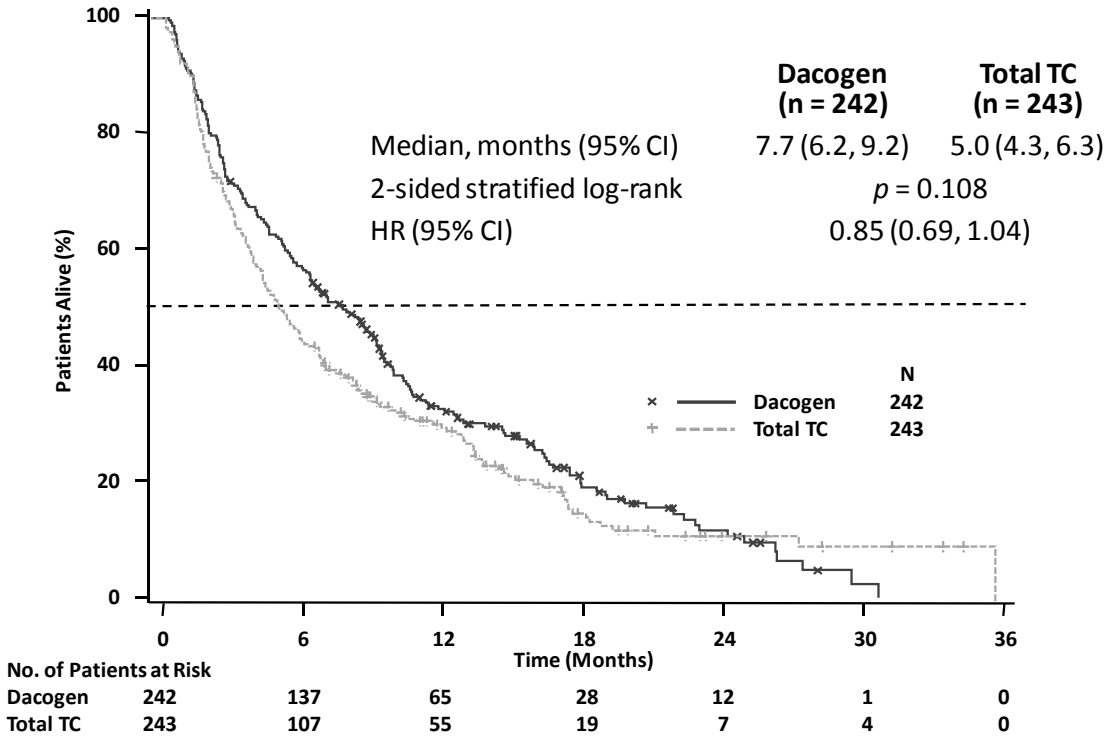
The primary population for all efficacy analyses was the intent to treat (ITT) population. Overall survival was calculated from the date of randomization to the date of death from any cause. Only one patient in each treatment arm was lost to survival follow-up.

5.4.1 Primary Endpoint: Overall Survival

The primary analysis of OS was planned to occur at 385 deaths, which was estimated to occur at the data cutoff date of 28 October 2009 (approximately 6 months after the last patient was enrolled). As of that date, 439 (90.5%) patients had discontinued treatment, of whom 396 (81.6%) patients had died, and 46 (9.5%) patients were continuing on study treatment. At the time of the database lock, there were 197 deaths in the Dacogen arm and 199 deaths in the TC arm.

Median OS in the ITT population was 7.7 months (95% CI: 6.2, 9.2 months) in the Dacogen arm compared with 5.0 months (95% CI: 4.3, 6.3 months) in the TC arm (Figure 3). The stratified hazard ratio (Dacogen arm/TC arm) was 0.85 (95% CI: 0.69, 1.04), and the stratified log-rank *p* value was 0.108. Although not statistically significant, the result represents a clinically meaningful trend for improvement in survival and a 15% reduction in the risk of death for patients treated with Dacogen.

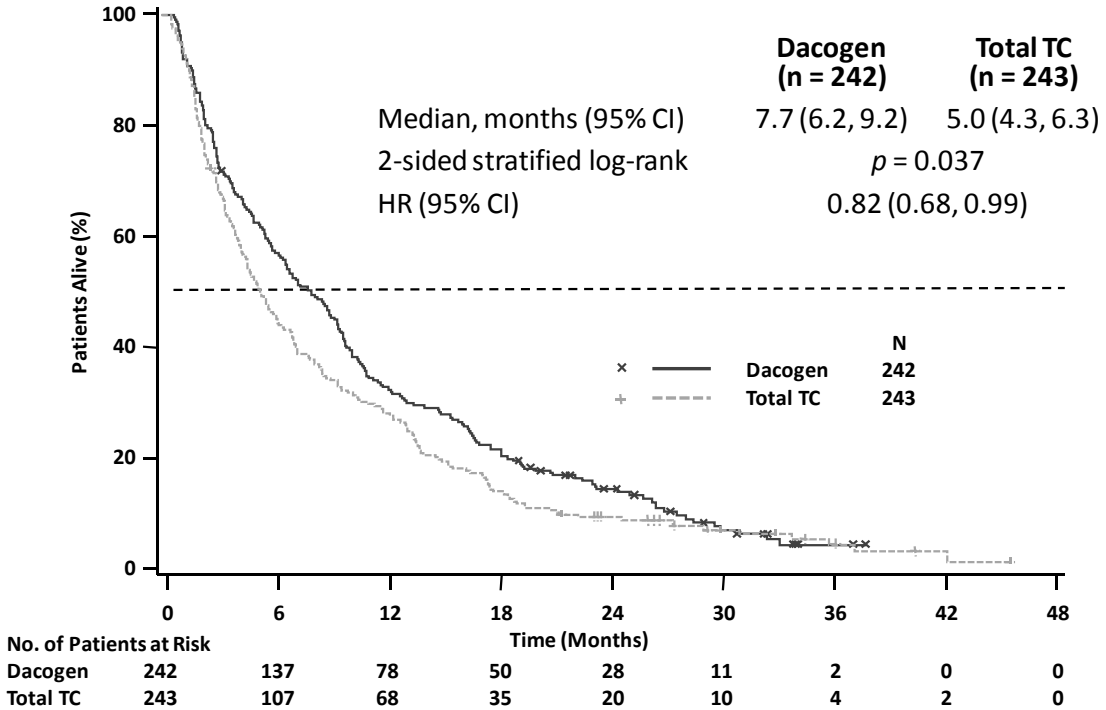
Figure 3 Kaplan-Meier Estimate of Overall Survival in Study 016, ITT Population (Cutoff: 28 October 2009).



5.4.1.1 Updated Analysis (Cutoff: 29 October 2010)

A single, unplanned, updated analysis of OS was performed and incorporated 1 additional year of follow-up (29 October 2010 data cutoff date). As of that date, 446 deaths (92.0%) had occurred (227 in the TC arm and 219 in the Dacogen arm). The median OS was 7.7 months (95% CI: 6.2, 9.2 months) in the Dacogen arm compared with 5.0 months (95% CI: 4.3, 6.3 months) in the TC arm (Figure 4). The stratified hazard ratio (Dacogen arm/TC arm) was 0.82 (95% CI: 0.68, 0.99), and the stratified log-rank nominal *p* value was 0.037, indicating an 18% absolute reduction in the risk of death for patients treated with Dacogen.

Figure 4 Kaplan-Meier Estimate of Overall Survival in Study 016, ITT Population (Cutoff: 29 October 2010).



5.4.2 Subsequent Disease-Modifying Therapy

A total of 75 patients received post-study DMT with either standard induction chemotherapy or a DNA hypomethylating agent (Table 9). Approximately 10% of patients in both arms received induction chemotherapy. However, there was an imbalance between arms in the proportion of patients who received subsequent treatment with a hypomethylating agent (5-azacytidine or Dacogen). In the TC arm, 19 (7.8%) patients received a hypomethylating agent compared with only 6 (2.5%) patients in the Dacogen arm.

Table 9 Subsequent Disease-Modifying Therapy

Type of subsequent therapy	Dacogen (N = 242)	Total TC (N = 243)
Induction chemotherapy	25 (10.3)	25 (10.3)
Hypomethylating agents	6 (2.5)	19 (7.8)
5-azacitidine	4 (1.7)	14 (5.8)
Dacogen	2 (0.8)	5 (2.1)

Abbreviations: TC = patient's choice of treatment with the advice of their physician.
Source: 016 CSR Table 21 p 92.

5.4.2.1 Sensitivity Analyses

The Committee for Medicinal Products for Human Use (CHMP) in the European Union recommended a sensitivity analysis to determine the influence of subsequent DMT on OS. Therefore, additional analyses of OS were performed as follows:

1) ITT analyses censoring or excluding patients who received subsequent DMT
2) ITT analyses censoring or excluding patients who received subsequent hypomethylating agents (5-azacitidine or Dacogen)
3) A per-protocol analysis of OS excluding patients who did not receive at least 2 cycles of study drug or had major protocol deviations

Censoring for Subsequent DMT

The analysis of OS censored for the use of subsequent DMT (including hypomethylating agents) demonstrated the treatment effect of Dacogen compared with TC (Table 10 and Figure 5). Median OS was 8.5 months in the Dacogen arm compared with 5.3 months in the TC arm (nominal $p = 0.044$), representing a 20% reduction in the risk of death (hazard ratio = 0.80). The other analyses either censoring or excluding patients who received subsequent DMT or hypomethylating agents showed consistent results favoring Dacogen.

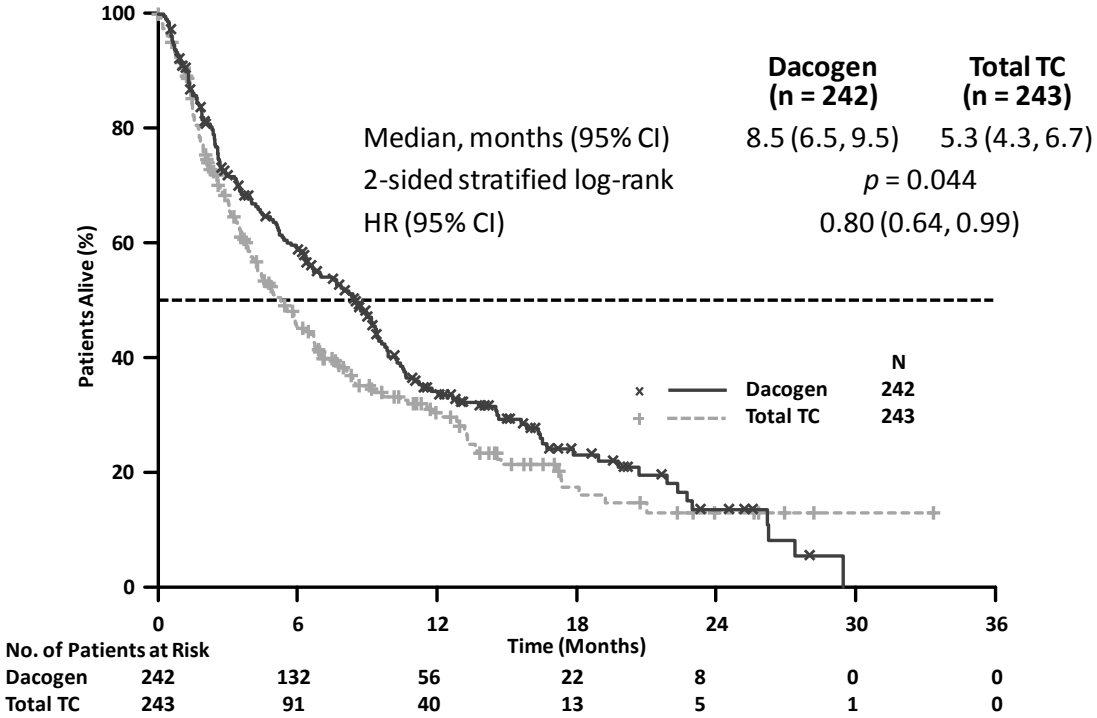
Table 10 Sensitivity Analysis of Overall Survival Censored for Subsequent Disease-Modifying Therapy (Cutoff: 28 October 2009)

Analysis	Dacogen (N = 242)	Total TC (N = 243)
ITT censored for subsequent DMT		
Median (95% CI)	8.5 (6.5, 9.5)	5.3 (4.3, 6.7)
Hazard ratio (95% CI)	0.80 (0.64, 0.99)	
Stratified log-rank, nominal *p* value	0.044	
ITT excluding patients with subsequent DMT	**n = 211**	**n = 199**
Median (95% CI)	7.0 (5.4, 9.0)	4.3 (3.5, 5.3)
Hazard ratio (95% CI)	0.74 (0.59, 0.92)	
Stratified log-rank, nominal *p* value	0.006	
ITT censored for subsequent HMAs		
Median (95% CI)	8.0 (6.0, 9.3)	4.9 (4.1, 6.0)
Hazard ratio (95% CI)	0.82 (0.67, 1.01)	
Stratified log-rank, nominal *p* value	0.063	
ITT excluding patients with subsequent HMAs	**n = 236**	**n = 224**
Median (95% CI)	7.9 (6.0, 9.3)	4.5 (3.8, 5.5)
Hazard ratio (95% CI)	0.77 (0.62, 0.94)	
Stratified log-rank, nominal *p* value	0.011	

Abbreviations: TC = patient's choice of treatment with physician's advice; DMT = disease-modifying therapy; HMAs = hypomethylating agents.

Source: Study 016 CSR Table 22, p 93; Tables teff04ax-rk and deff48x-rk.

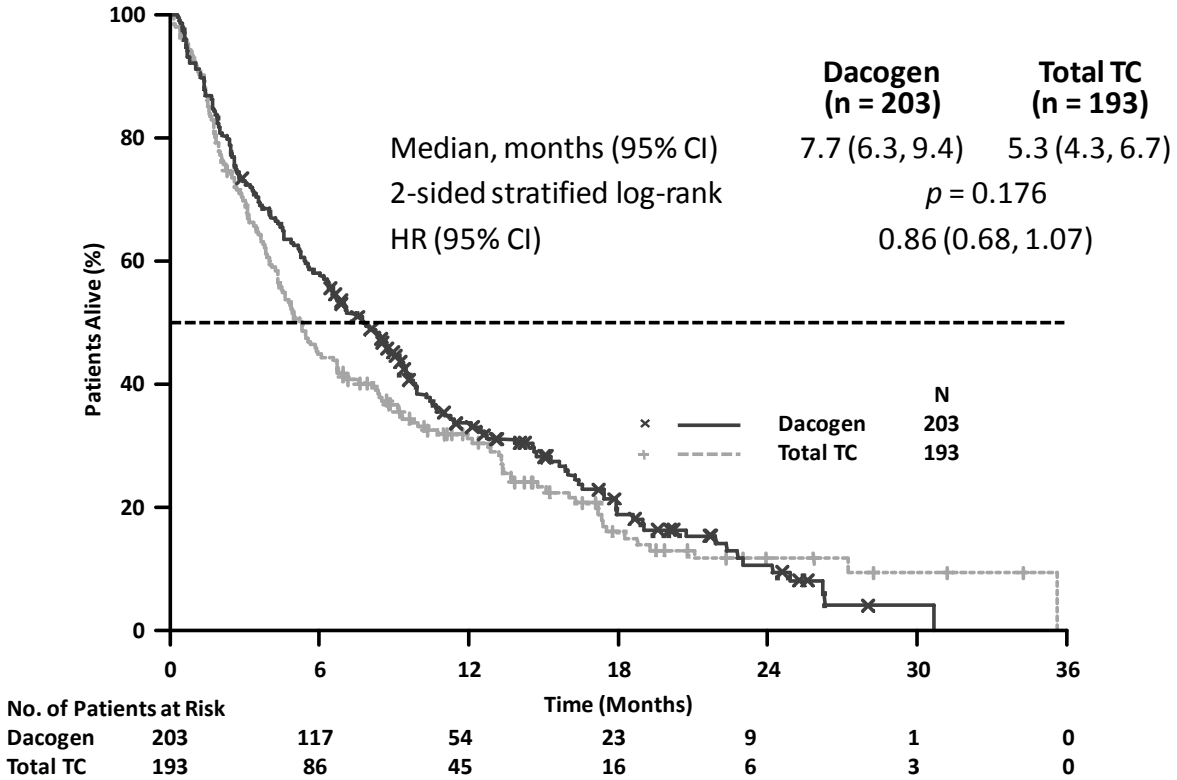
Figure 5 Kaplan-Meier Estimate of Overall Survival in Study 016 Censored for Subsequent Disease-Modifying Therapy, ITT Population (Cutoff: 28 October 2009).



Per-Protocol Analysis

An analysis of OS in the PP population was performed as originally planned. The PP analysis set included 396 patients (203 in the Dacogen arm and 193 in the TC arm) and was used for sensitivity analyses of selected efficacy endpoints. The results of the analysis of OS for the PP population were consistent with those of the ITT population, demonstrating a median OS of 7.7 months in the Dacogen arm compared with 5.3 months in the TC arm (Figure 6).

Figure 6 Kaplan-Meier Estimate of Overall Survival in Study 016, Per-Protocol Population (Cutoff: 28 October 2009).



5.4.2.2 Subgroup Analyses for Overall Survival

Pre-specified OS analyses by subgroup were performed with both 2009 data cutoff (Figure 7) and 2010 data cutoff (Figure 8). The majority of subgroups demonstrated a consistent treatment effect of Dacogen compared with TC.

Figure 7 Overall Survival by Subgroup in Study 016, ITT Population (Cutoff: 28 October 2009).

Subgroup	HR (95% CI)	Total TC Event/N	Total TC Med	Dacogen Event/N	Dacogen Med	*p* value
All patients	0.85 (0.69, 1.04)	199/243	5.0	197/242	7.7	0.108
Age (years)						
< 70	0.99 (0.67, 1.46)	53/70	4.9	58/71	8.7	0.950
70-74	0.79 (0.55, 1.15)	59/74	5.7	61/76	8.0	0.221
≥ 75	0.78 (0.57, 1.07)	87/99	4.5	78/95	6.3	0.125
Type of AML						
De novo AML	0.73 (0.57, 0.95)	130/157	5.2	125/155	8.0	0.018
Secondary AML	0.91 (0.6, 1.30)	64/68	4.9	72/87	7.1	0.605
Baseline bone marrow blasts (%)						
≥ 20 to ≤ 30	1.09 (0.71, 1.67)	41/58	6.1	53/65	8.0	0.711
> 30	0.74 (0.58, 0.94)	150/175	4.3	139/172	7.1	0.013
Baseline cytogenetic risk						
Intermediate risk	0.79 (0.61, 1.02)	121/154	6.0	118/152	9.4	0.071
Poor risk	0.92 (0.66, 1.27)	77/87	3.1	77/87	5.7	0.590
Baseline ECOG PS						
0-1	0.90 (0.71, 1.14)	141/178	6.1	147/182	8.7	0.387
2	0.71 (0.48, 1.06)	58/65	3.6	50/60	5.3	0.093
Region						
N. America/Australia	0.91 (0.60, 1.36)	63/69	4.9	45/51	6.0	0.631
Eastern Europe	0.73 (0.54, 1.00)	91/113	4.3	89/109	6.7	0.048
Western Europe	1.43 (0.79, 2.60)	22/34	14.4	40/51	9.1	0.239
Asia	0.83 (0.44, 1.56)	23/27	4.5	23/31	9.3	0.552

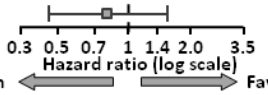
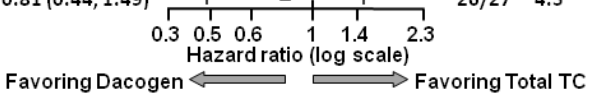


Figure 8 Overall Survival by Subgroup in Study 016, ITT Population (Cutoff: 29 October 2010).

Subgroup	HR (95% CI)	Total TC Event/N	Total TC Med	Dacogen Event/N	Dacogen Med	*p* value
All patients	0.82 (0.68, 0.99)	227/243	5.0	219/242	7.7	0.037
Age (years)						
< 70	1.01 (0.70, 1.45)	62/70	4.9	65/71	9.1	0.961
70-74	0.79 (0.56, 1.11)	69/74	5.7	69/76	8.0	0.165
≥ 75	0.72 (0.54, 0.98)	96/99	4.5	85/95	6.3	0.035
Type of AML						
De novo AML	0.71 (0.56, 0.91)	149/157	5.2	137/155	8.2	0.006
Secondary AML	0.92 (0.66, 1.29)	77/84	4.9	82/87	7.1	0.636
Baseline bone marrow blasts (%)						
≥ 20 to ≤ 30	1.12 (0.76, 1.66)	52/58	6.1	60/65	8.0	0.574
> 30	0.72 (0.57, 0.91)	166/175	4.3	154/172	7.1	0.005
Baseline cytogenetic risk						
Intermediate risk	0.78 (0.61, 0.99)	142/154	6.0	135/152	9.4	0.044
Poor risk	0.87 (0.63, 1.19)	84/87	3.1	82/87	5.7	0.373
Baseline ECOG PS						
0-1	0.88 (0.71, 1.10)	163/178	6.1	165/182	8.6	0.273
2	0.65 (0.44, 0.95)	64/65	3.6	54/60	5.3	0.025
Region						
N. America/Australia	0.93 (0.63, 1.38)	65/69	4.9	47/51	6.0	0.727
Eastern Europe	0.75 (0.56, 1.00)	106/113	4.3	101/109	6.7	0.046
Western Europe	1.03 (0.62, 1.72)	30/34	12.5	43/51	9.0	0.909
Asia	0.81 (0.44, 1.49)	26/27	4.5	28/31	9.3	0.499



5.4.2.3 Comparability of Geographic Regions

The FDA raised variability in the OS benefit by geographic region as a review issue. As seen in the forest plot in Figure 7, OS in the small subgroup of patients treated in Western Europe showed a hazard ratio that appeared to favor the TC arm (HR = 1.43). However, with the addition of more events in the updated analysis of OS, the hazard ratio in this subgroup was 1.03 (Figure 8). To understand this better, additional exploratory analyses were performed.

Kaplan-Meier analysis of OS by region revealed that patients randomized to Dacogen had similar survival outcomes across regions (Figure 9). In the TC arm, patients treated in Asia, Eastern Europe, and North America/Australia all had similar survival outcomes. However, patients randomized to the TC arm in Western Europe (n = 34) had unusually favorable survival outcomes compared with the other geographic regions (Figure 9). Of note, a much higher proportion of patients in Western Europe randomized to the TC arm (35%) received subsequent treatment with a hypomethylating agent (mostly 5-azacytidine) compared with only 8% in the Dacogen arm (Table 11). In the other geographic regions, use of post-study hypomethylating agents was infrequent. This could have contributed to the anomalous OS in the TC arm in Western Europe. As an additional note, the number of patients in Western Europe was relatively small, and there was a numerical imbalance in patients assigned to each treatment arm (51to the Dacogen arm versus 34 to the TC arm).

Figure 9 Overall Survival by Geographic Regions for Patients Randomized to Dacogen or TC Arms (Cutoff: 29 October 2010).

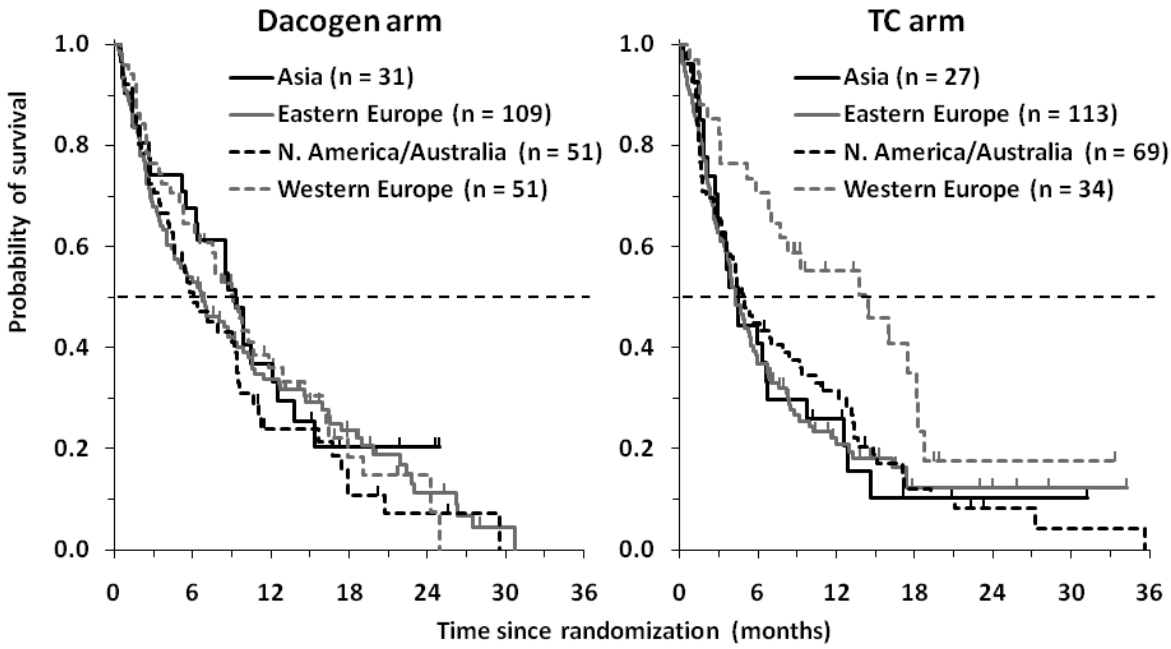


Table 11 Subsequent Use of Hypomethylating Agents by Geographic Region

	Patients, n (%)	
Region	**Dacogen**	**Total TC**
Western Europe	4/51 (7.8)	12/34 (35.3)
North America/Australia	2/51 (3.9)	7/69 (10.1)
Eastern Europe	0	0
Asia	0	0

In contrast to Western Europe, the hazard ratios for OS in the other regions generally favored Dacogen, with the largest benefit observed in Eastern Europe and Asia (see Figures 7 and 8). Importantly, there were no gross differences in patient characteristics or prognostic scores for patients in Eastern Europe and Asia compared with North America/Australia (Table 12). However, patients in Eastern Europe and Asia did not receive any post-study treatment with hypomethylating agents, whereas patients in North America/Australia did (Table 11). Thus, Eastern Europe and Asia may represent a purer assessment of the Dacogen treatment effect without the potential confounding effects of imbalances in post-study therapy. Nevertheless, the results remain comparable and generalizable across these regions.

Table 12 Comparison of Patients by Geographic Region

Characteristic	**Eastern Europe (n = 222)**	**N Am/Australia (n = 120)**	**Western Europe (n = 85)**	**Asia (n = 58)**
Median age, years (range)	71 (64 - 89)	76 (64 - 89)	74 (65 - 85)	73 (64 - 91)
ECOG PS, n (%)				
0	16 (7.2)	34 (28.3)	34 (40.0)	5 (8.6)
1	132 (59.5)	65 (54.2)	39 (45.9)	35 (60.3)
2	74 (33.3)	21 (17.5)	12 (14.1)	18 (31.0)
Type of AML, n (%)				
de novo	164 (73.9)	66 (55.0)	49 (57.6)	33 (56.9)
Secondary	58 (26.1)	53 (44.2)	35 (41.2)	25 (43.1)
Cytogenetic risk group, n (%)				
Intermediate	142 (64.3)	70 (58.8)	51 (60.0)	43 (74.1)
Unfavorable	79 (35.7)	49 (41.2)	31 (36.5)	15 (25.9)
Median WBC count, $10^3/\mu L$ (range)	3.9 (0.5 - 126.6)	2.9 (0.3 - 75.5)	2.8 (0.5 - 95.6)	4.0 (0.3 - 25.4)
Mean blasts in marrow (SD)	50.7 (23.28)	51.5 (24.13)	47.6 (24.11)	47.2 (23.25)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; N Am = North America; SD = standard deviation; WBC = white blood cell.

Source: tsub02, tsub20, tsub21 for each region.

5.4.3 Secondary Efficacy Endpoints

5.4.3.1 Complete Remission Rate

Based on the IRC assessment, a significantly higher proportion of patients in the Dacogen arm (17.8%) achieved CR + CRp compared with patients in the TC arm (7.8%). The odds ratio for CR + CRp (Dacogen arm/TC arm) was 2.5; $p = 0.001$) favoring the Dacogen arm (Table 13). The CR rate in the Dacogen arm was also significantly higher than in the TC arm ($p = 0.004$). All responses in the TC arm occurred in patients treated with cytarabine.

In addition to the protocol-defined secondary endpoint, response assessments were also made by the investigators according to IWG 2003 criteria. Assessment by the investigator showed a 14% rate of CR + CRp in the Dacogen arm compared with 9% in the TC arm. A concordance rate of approximately 76% was observed between the IRC and investigator assessments in both the Dacogen and TC arms.

Table 13 Best Response by Independent Review Committee and Investigator (Study 016)

	Patients, n (%)			
	IRC Assessment		Investigator Assessment	
	Dacogen (N = 242)	Total TC (N = 243)	Dacogen (N = 242)	Total TC (N = 243)
CR	38 (15.7)	18 (7.4)	28 (11.6)	19 (7.8)
CRi	24 (9.9)	7 (2.9)		
CRp	5 (2.1)	1 (0.4)	6 (2.5)	3 (1.2)
CR + CRp	**43 (17.8)**	**19 (7.8)**	**34 (14.0)**	**22 (9.1)**
Odds ratio (95% CI)	**2.5 (1.40, 4.78)**		**1.6 (0.90, 3.05)**	
***p* value**	**0.001**		**0.090**	

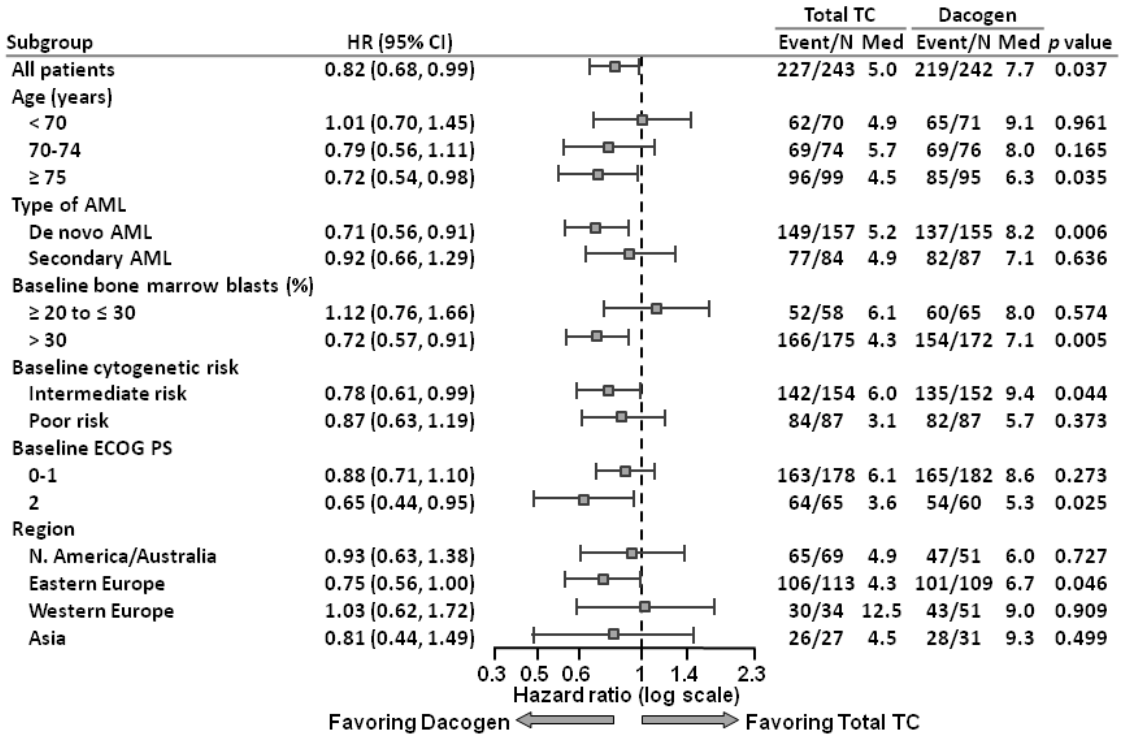
Abbreviations: CR = morphologic complete remission; CRi = CR with incomplete blood count recovery; CRp = CR with incomplete platelet recovery; TC = patient's choice of treatment with physician's advice.

Source: SCE Table 14 p 34. CSR Table 14.2.18 p 468.

5.4.3.2 Subgroup Analyses for Complete Remission

Analysis of CR + CRp in the pre-specified subgroups demonstrated a consistent advantage in favor of Dacogen, including patients with secondary AML, baseline bone marrow blast counts > 30%, and poor-risk cytogenetics (Figure 10).

Figure 10 Complete Remission (CR + CRp) by Subgroup in Study 016.



Abbreviation: NE = not evaluable.

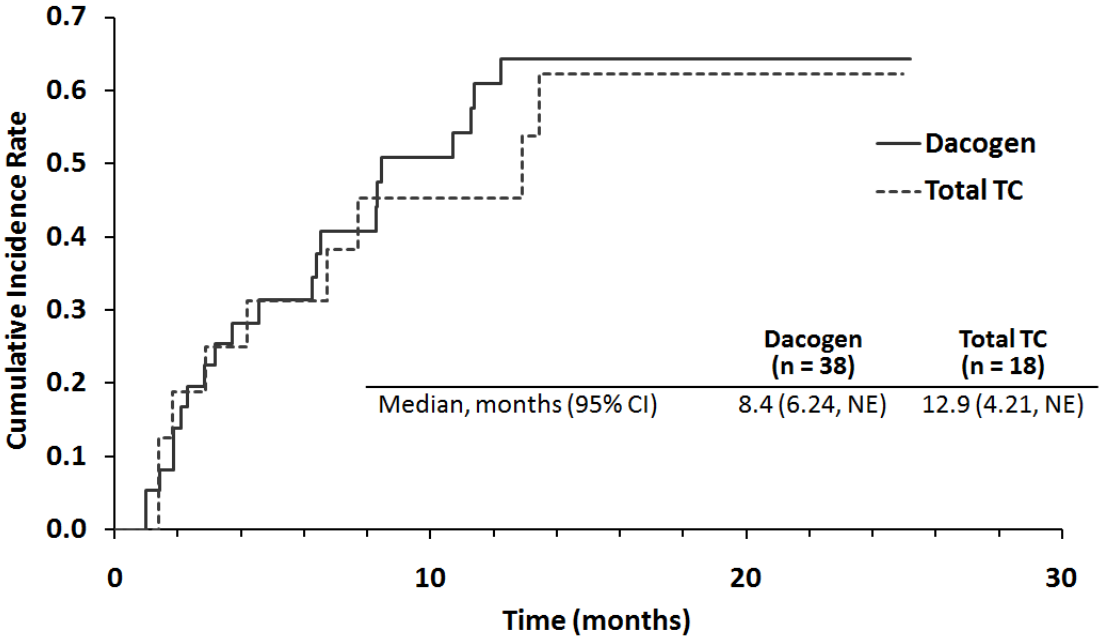
5.4.3.3 Duration of Response and Relapse-Free Survival

Median duration of best response (CR + CRp) was 8.3 months (95% CI: 6.2, 11.4) in the Dacogen arm compared with 12.9 months (95% CI: 4.2, not estimable) in the TC arm based on the defined assessment criteria. However, this measure of response duration is potentially confounded by censoring. Duration of best response was defined as the number of months from the date of best response (CR or CRp) until relapse ([date of relapse – date of best response + 1]/30.4375). For patients who died without relapse, duration of response was right-censored at the date of death, which is consistent with the published IWG criteria for AML.[32] For patients without a recorded date of death or relapse, duration of response was censored at the last disease assessment date (i.e., the last hematology sample date or the last bone marrow sample date, whichever occurred later).

Cumulative Incidence of Relapse

Cumulative incidence of relapse was also assessed in patients achieving a CR. This is an alternative analysis that was suggested in the IWG 2003 publication.[32] This analysis shows that when patients achieved CR with either Dacogen or cytarabine (i.e., Total TC), they remained in remission for approximately the same amount of time (Figure 11).

Figure 11 Cumulative Incidence of Relapse in Study 016.



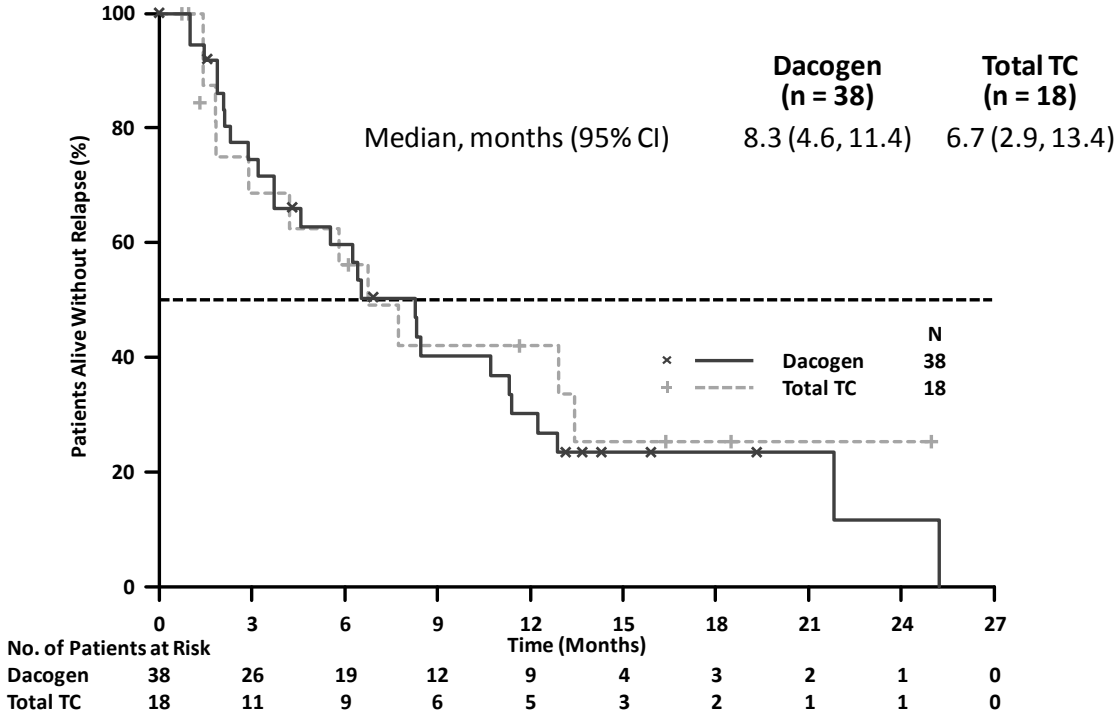
Abbreviation: NE = not evaluable.

Relapse-free Survival

Median relapse-free survival (RFS) may be a more clinically meaningful measure than duration of response because it avoids censoring pitfalls. RFS was calculated only for those patients in the ITT population who achieved a morphologic CR. The median RFS for this subset of patients was 8.3 months (95% CI: 4.6, 11.4) in the Dacogen arm compared with 6.7 months (95% CI: 2.9, 13.4) in the TC arm (Figure 12). These analyses were based on a subgroup defined by an outcome variable (i.e., response). Hence, any formal comparison between the two treatment arms would not be appropriate. The results of the RFS analysis for the PP population were consistent with those of the ITT population.

Another measure of the durability of response is the proportion of responses that were maintained for at least 90 days (Deisseroth FDA presentation 2009). Indeed, the majority of CR and CRp were durable for at least 90 days (28/43 [65.1%] in the Dacogen arm and 12/19 [63.2%] in the TC arm).

Figure 12 Kaplan-Meier Estimate of Relapse-Free Survival Among Patients with a Morphologic Complete Remission (ITT Population).

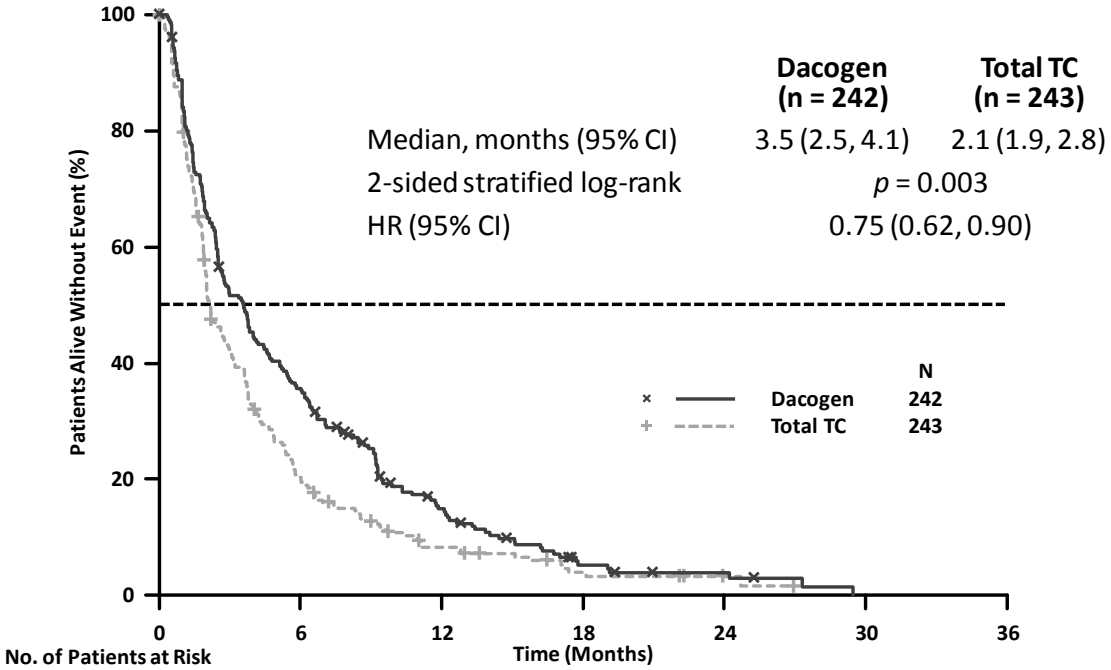


5.4.3.4 Time to Event Analyses

Event-free Survival

A total of 223 patients (92.1%) in the Dacogen arm and 224 patients (92.2%) in the TC arm (ITT population) experienced a protocol-defined event for the determination of EFS (disease progression, relapse from a morphologic CR, or death after discontinuation from study treatment). In the Dacogen and TC arms, respectively, 159 (65.7%) and 163 (67.1%) patients experienced treatment failure, 37 (15.3%) and 14 (5.8%) patients experienced relapse from a morphologic CR, and 27 (11.2%) and 47 (19.3%) patients died after discontinuation from study treatment. Median EFS time was significantly longer for patients in the Dacogen arm (3.5 months) compared with the TC arm (2.1 months) (Figure 13).

Figure 13 Kaplan-Meier Estimate of Event-Free Survival in Study 016, ITT Population (Cutoff: 28 October 2009).

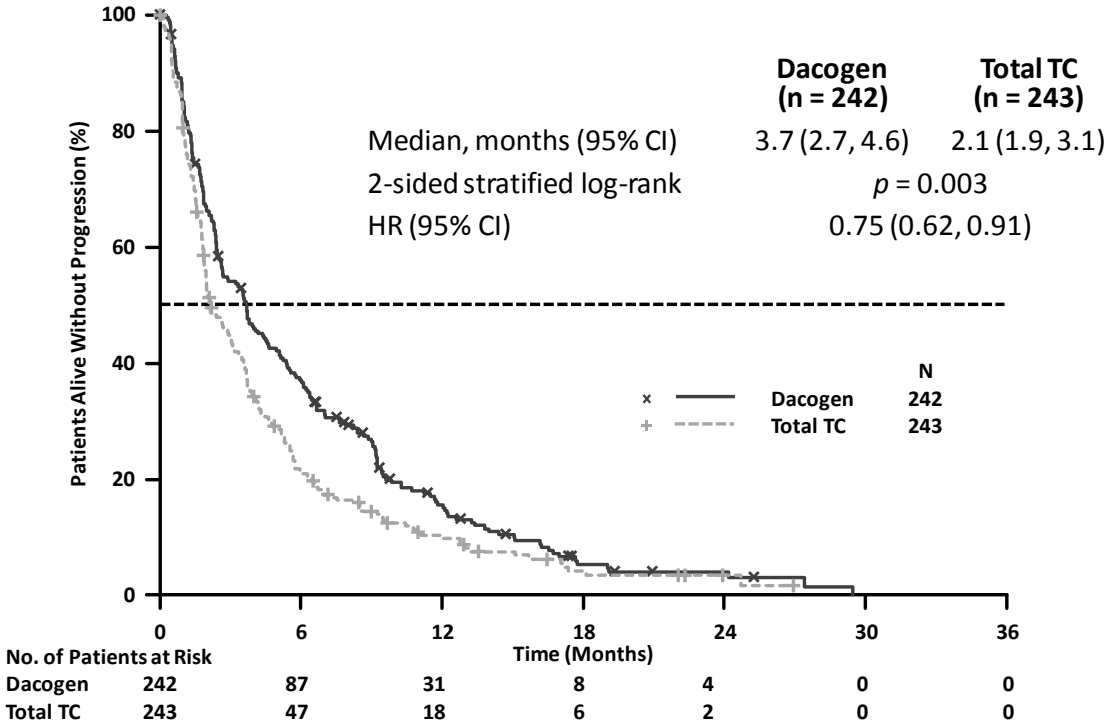


No. of Patients at Risk							
Dacogen	242	87	31	8	4	0	0
Total TC	243	47	18	6	2	0	0

Progression-free Survival

A total of 221 patients (91.3%) in the Dacogen arm and 221 patients (90.9%) in the TC arm experienced a protocol-defined disease progression event (disease progression as defined in Table 4 or death). In the Dacogen and TC arms, respectively, 135 (55.8%) and 130 (53.5%) patients had disease progression, and 86 (35.5%) and 91 (37.4%) patients died. Median PFS time was significantly longer for patients in the Dacogen arm (3.7 months) compared with the TC arm (2.1 months) (Figure 14).

Figure 14 Kaplan-Meier Estimate of Progression-Free Survival in Study 016, ITT Population (Cutoff: 28 October 2009).



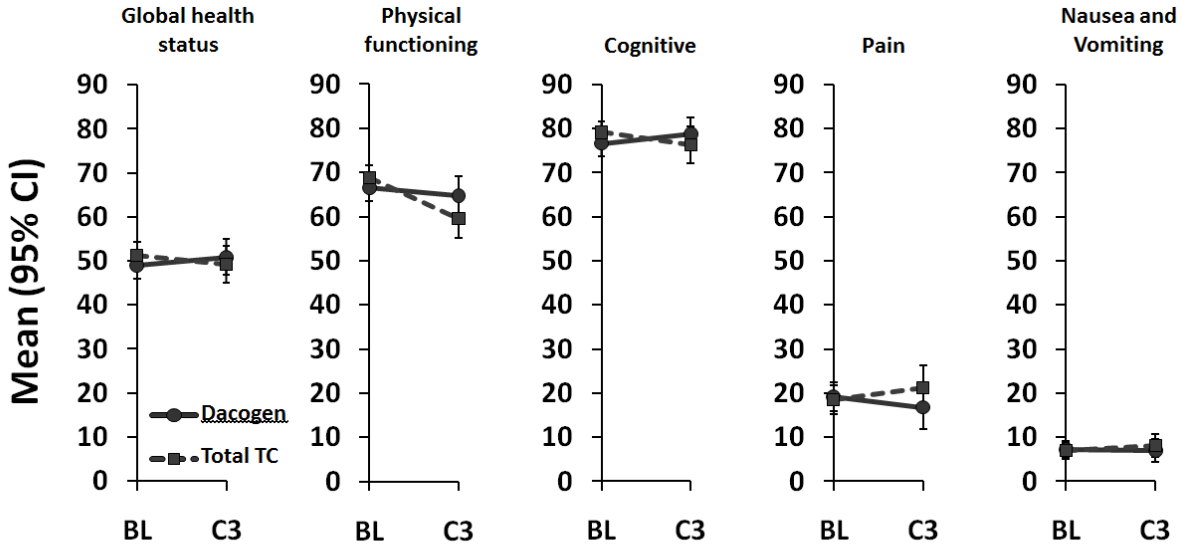
5.4.3.5 Cytogenetic Response Rate

The cytogenetic complete remission (CRc) rate was evaluated in patients who had a cytogenetic abnormality at baseline, had documented CR or CRp on study, and had a cytogenetic assessment performed after documented CR or CRp. Only approximately 50% of patients who achieved CR had abnormal cytogenetics at baseline. However, the majority of those patients did not have cytogenetic assessments performed after CR was reported. Among patients who met all criteria for CRc evaluation, 4 patients in the Dacogen arm and 3 patients in the TC arm with CR or CRp had a reversion to a normal karyotype and were, therefore, reconsidered to have achieved CRc.

5.4.3.6 Overall Quality of Life

Overall QoL and the Fatigue Subscale Score using the EORTC QLQ-C30 questionnaire were assessed before randomization, on Day 1 of Cycles 3, 4, and 6, and at the end of study treatment. The intent was to compare the incidence of patients with a > 10-point change from pre-randomization to Cycle 3 between treatment groups. However, due to deaths, study discontinuations, and missing values, only 118 patients (48.8%) in the Dacogen arm and 109 patients (44.9%) in the TC arm were evaluable for analysis of global health status at Cycle 3. In light of this, the available data must be interpreted with caution, and one cannot draw definitive conclusions. However, the available data from patients who did complete the Cycle 3 assessment show that there was no adverse effect of Dacogen on QoL (Figure 15). For Global Health Status and functional subscales, higher scores indicate better QoL. For symptom scales such as pain and nausea/vomiting, a lower score indicates fewer symptoms.

Figure 15 Change in Quality of Life Score From Baseline to Cycle 3.



Patients, n	Global health status BL	Global health status C3	Physical functioning BL	Physical functioning C3	Cognitive BL	Cognitive C3	Pain BL	Pain C3	Nausea and Vomiting BL	Nausea and Vomiting C3
Dacogen	228	118	228	118	228	118	228	118	228	117
Total TC	226	109	224	111	226	111	226	111	226	111

Abbreviations: BL = baseline; C3 = Cycle 3.

6.0 SUMMARY OF CLINICAL EFFICACY IN SUPPORTIVE STUDY 017

6.1 Study Design

Study 017 was conducted in the United States and was an open-label, single-arm, multicenter Phase 2 trial in elderly patients (age ≥ 60 years) with de novo or secondary AML and intermediate- or unfavorable-risk cytogenetics. Apart from the lower age limit, the population enrolled in Study 017 was very similar to that enrolled in Study 016. Patients enrolled in this study were not candidates for standard induction chemotherapy, bone marrow or stem cell transplant, gemtuzumab ozogamicin), or all-transretinoic acid for their disease. All FAB subtypes of AML were acceptable for this trial except promyelocytic leukemia (M3 classification).

Treatment consisted of Dacogen 20 mg/m^2 given as a 1-hour i.v. infusion once daily on days 1 - 5 of each 4-week cycle. Study treatment was continued as long as the patient derived benefit according to the clinical judgment of the investigator. Patients were followed for 30 days after the date of the last Dacogen dose to monitor for toxicity, patient status, and relapse, if applicable. Thereafter, patients were followed every 2 months until death, loss to follow-up, or study closure.

The primary efficacy endpoint was the rate of morphologic CR in the ITT population. Independent external leukemia experts determined responses based on the IWG 2003 criteria. Overall survival was a secondary endpoint.

6.1.1 Demographics and Baseline Disease Characteristics

The demographic and baseline disease characteristics of patients enrolled in Study 017 were similar to those of patients randomized to Dacogen in Study 016 (Table 14). Importantly, although the minimum age for enrollment in Study 017 was 60 years, the median age of patients enrolled was nearly identical to that in Study 016. The only notable difference was that more patients in Study 017 had ECOG PS of 0 (47.3%) compared with the Dacogen arm in Study 016 (17.4%). Therefore, Study 017 is appropriate as a supportive study, and the patient population is representative of elderly patients with AML in the United States.

Table 14 Demographics and Baseline Disease Characteristics in Study 017 Compared with Study 016

Characteristic	Study 017 (N = 55)	Dacogen arm Study 016 (N = 242)
Median age, years (range)	74 (61-87)	73 (64-89)
Age category, n (%)		
< 65 years	7 (12.7)	3 (1.2)
65-74 years	23 (41.8)	144 (59.5)
≥ 75 years	25 (45.5)	95 (39.3)
Sex, n (%)		
Male	27 (49.1)	137 (56.6)
Female	28 (50.9)	105 (43.4)

Characteristic	Study 017 (N = 55)	Dacogen arm Study 016 (N = 242)
ECOG PS, n (%)		
0	26 (47.3)	42 (17.4)
1	19 (34.5)	140 (57.9)
2	10 (18.2)	60 (24.8)
Type of AML, n (%)		
de novo	30 (54.5)	155 (64.0)
Secondary	23 (41.8)	87 (36.0)
N/A	2 (3.6)	0
Cytogenetic classification of risk, n (%)		
Intermediate	29 (52.7)	152 (63.1)[a]
Unfavorable	25 (45.5)	87 (36.0)
N/A	0	2 (0.8)
Missing	1 (1.8)	0

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; AML = acute myelogenous leukemia; N/A = not available.
a: 241 patients were evaluable for cytogenic classification.
Source: Study 017 CSR Tables 10, 11 pages 52, 53.

6.1.2 Efficacy Results

In Study 017 the data cutoff date was February 1, 2008, which allowed all patients to have at least 1 year of follow-up on study. As of this date, a total of 50 (90.9%) of the 55 enrolled patients had discontinued treatment, 45 patients had died, and 5 patients (9.1%) continued to receive Dacogen.

6.1.2.1 Primary Endpoint

Morphologic CR, as assessed by the external expert reviewer for the ITT population, was achieved in 13 patients (23.6%) (Table 15). Of the 34 patients who had a cytogenetic abnormality at baseline, 5 (14.7%) achieved a cytogenetic CR. Median time to relapse for patients who achieved a morphologic CR, CRi, or CRc was 553 days (95% CI: 126, not estimable), which is approximately 18.2 months. Median EFS was 174 days (95% CI: 93, 246), which is approximately 5.7 months.

Table 15 Morphologic Best Response in Study 017, ITT Population

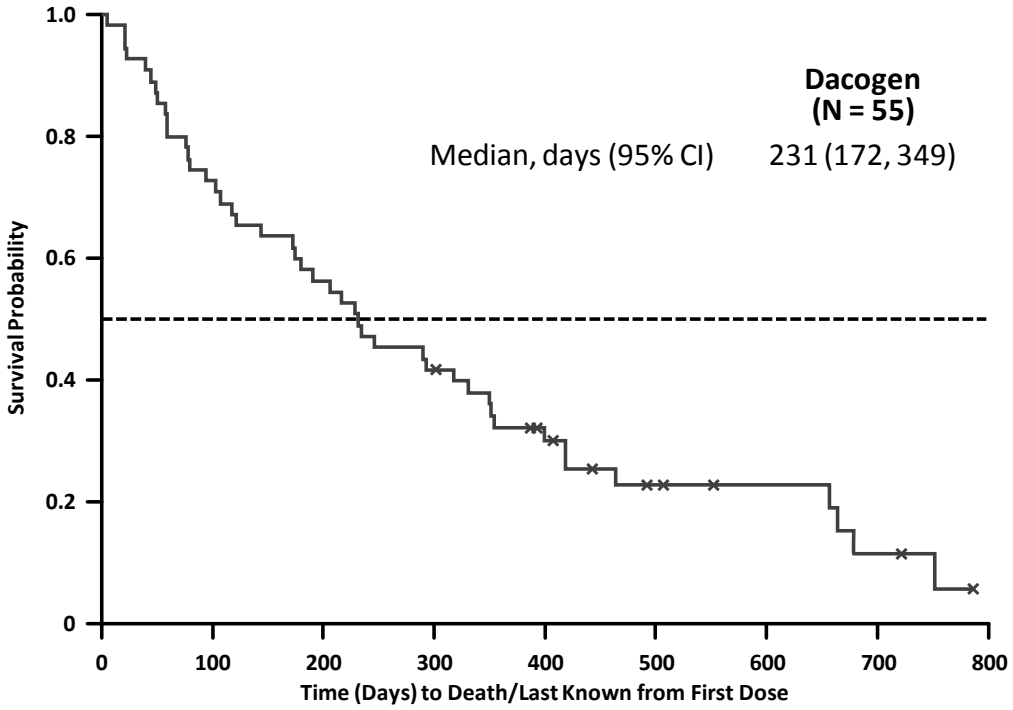
Response	Patients, n (%) (N = 55)	95% CI, %
CR	13 (23.6)	13.2, 37.0
CRc	5/34 (14.7)	5.0, 31.1
CRi	1 (1.8)	0.0, 9.7

Abbreviations: CR = complete remission; CRc = cytogenetic CR; CRi = morphologic CR with incomplete blood count recovery.
Source: 017 CSR pg 109. Table 14.2.1.1.1

6.1.2.2 Secondary Endpoints

Overall survival was a secondary endpoint in Study 017. As of the February 1, 2008 cutoff date, 45 of the 55 patients (81.8%) enrolled had a confirmed death, and 10 patients (18.2%) were known to be alive at their date of last contact. Median OS was 231.0 days (Figure 16), which is approximately 7.6 months. This is consistent with the median OS observed in the Dacogen arm of Study 016.

Figure 16 Kaplan-Meier Estimate of Overall Survival in Study 017, ITT Population.



6.1.3 Overall Efficacy Conclusions

Taken together, the clinical evidence of efficacy from Study 016 demonstrated that 20 mg/m^2 of Dacogen once daily for 5 consecutive days every 4 weeks is more effective than low-dose cytarabine or SC in this patient population. The pre-specified primary analysis demonstrated a 2.7-month improvement in median OS (7.7 months vs 5.0 months) that, although similar to the pre-study assumption (8 months versus 6 months), was not statistically significant. However, an unplanned OS analysis with 1 year of additional follow-up demonstrated the same improvement in median OS with a nominal *p* value of 0.037, which supports the conclusion that the OS difference observed in the primary analysis represents a real treatment effect. Sensitivity analyses of OS that adjusted for subsequent DMT demonstrated a significant OS advantage in favor of Dacogen, thus providing further support for the observation of a treatment effect in this patient population. Moreover, Dacogen significantly improved the rate of CR, CR + CRp, EFS, and PFS compared with TC. Taken together, these data provide evidence of a clinically meaningful treatment effect and support the clinical benefit of Dacogen in this setting. Additionally, the median OS and CR rate observed in supportive Study 017, which was conducted solely in the United States, were consistent with the benefit of Dacogen observed in Study 016.

7.0 SUMMARY OF CLINICAL SAFETY

This section presents the safety data from randomized Study 016 (updated 2010 data) and the supportive single-arm Study 017. The emphasis and in-depth analysis of safety is based on Study 016 data because of the larger study population and the availability of a comparator arm.

7.1 Safety Population (Study 016)

The safety population was defined as all patients in Study 016 who were assigned to study treatment and received any amount of study treatment. Patients who were randomly assigned to the TC arm in Study 016 and received SC only were also included in the safety population. The data cutoff date for the Safety Population was 29 October 2010. Patient disposition at that time is shown in Table 16.

Table 16 Patient Disposition (Cutoff: 29 Oct 2010)

	Patients, n (%)			
		Treatment Choice (TC)		
	Dacogen (N = 242)	Total TC (N = 243)	Cytarabine (N = 215)	SC (N = 28)
Treated	238 (98.3)	237 (97.5)	208 (96.7)	29 (103.6)
Discontinued	235 (97.1)	240 (98.8)	212 (98.6)	28 (100.0)
Ongoing at database lock	7 (2.9)	3 (1.2)	3 (1.4)	0
Reason for discontinuation of treatment				
Progressive disease	106 (45.1)	119 (49.6)	115 (54.2)	4 (14.3)
Adverse event	26 (11.1)	31 (12.9)	30 (14.2)	1 (3.6)
Patient decision	19 (8.1)	15 (6.3)	5 (2.4)	10 (35.7)
Non-compliance	1 (0.4)	3 (1.3)	1 (0.5)	2 (7.1)
Death	63 (26.8)	44 (18.3)	36 (17.0)	8 (28.6)
Lost to follow-up	0	0	0	0
Investigator decision	12 (5.1)	16 (6.7)	16 (7.5)	0
Other	8 (3.4)	12 (5.0)	9 (4.2)	3 (10.7)
Patient consent withdrawn	0	0	0	0

Abbreviations: SC = supportive care; TC = patient's choice of treatment with the advice of their physician
Source: SCE Table 8 pg 26.

7.2 Extent of Exposure

Patients received a median of 4.0 cycles (range, 1 – 33) of Dacogen compared with a median of 2.0 cycles (range, 1 – 41) of cytarabine (Table 17). Thus, the median duration of treatment was approximately 2-fold longer for Dacogen than for cytarabine (median, 4.4 versus 2.4 months). Given that AEs were collected only during treatment and for 30 days after discontinuation of study treatment, the safety reporting period was substantially longer in the

Dacogen arm. This information must be considered when interpreting the results of the safety analyses.

Table 17 Summary of Exposure to Cytarabine and Dacogen (Study 016 Safety Population)

Exposure Parameter	Dacogen[a] N = 238	Cytarabine[a] N = 208
Total number of cycles	1,706	991
% Cycles in which patients received all planned infusions	(97.8%)	(94.2%)
Total number of cycles received per patient		
Median	4.0	2.0
Min – Max	1.0 – 33.0	1.0 – 41.0
Relative dose intensity (DI ÷ PDI)[b]		
Median	0.97	0.98
Min – Max	0.48 – 1.11	0.18 – 2.00
Total duration of treatment, months[c]		
Median	4.4	2.4
Min – Max	0.3 – 33.7	0.1 – 39.8

Abbreviations: DI = dose intensity; max = maximum; min = minimum; PDI = planned dose intensity.
a: Planned Dose Intensity = 50 mg /m^2/wk (cytarabine) and 25 mg /m^2/wk (Dacogen).
b: Dose intensity was calculated as daily dose ÷ BSA for each cycle, then summed over all cycles for each patient, then divided by study duration of each patient.
c: The duration of treatment = (last dose – first dose) + 28 for the 5-day Dacogen dosing regimen.
Source: ISS Table 2.1.1; ISS Table 2.3; SCS Table 2, p 22

7.3 Adverse Events

Adverse events (AEs) were defined as any unfavorable change in physical sign, symptom, or clinically significant laboratory change occurring immediately after the patient was randomly assigned to a treatment group, regardless of its relationship to study drug. Because of this, not all recorded AEs were necessarily treatment-emergent. In reviewing the safety data, the following points may be helpful to consider:

- Adverse events were captured from the time a patient was randomized until 30 days after the patient discontinued study treatment. Patients were followed until the event resolved or reached a medically acceptable outcome, or the patient was lost to follow-up. After the 30-day post-treatment period, only treatment-related events (new or continuing) were reported or followed until resolution, acceptable medical outcome, or loss to follow-up.
- Adverse events were collected, and are presented, without regard to assessment of causal relationship to study drug.
- The AEs presented in this section are treatment-emergent AEs (TEAEs), that is, they occurred after study treatment was initiated, or in the case of patients receiving SC, after randomization. Therefore, if a patient had neutropenia at baseline, only new or worsening neutropenia during study treatment or within 30 days of last dose of study drug would be considered a TEAE.

- Except where otherwise specified, AEs are reported without correction for differences in the observation period for AEs between treatment arms.
- For completeness, safety data are presented for the entire randomized control group (Total TC) and for the subgroups of patients within the TC arm who received either cytarabine or SC.

A serious adverse event (SAE) was defined as any adverse experience that resulted in death; was life threatening; required inpatient hospitalization or prolongation of a hospitalization; resulted in persistent or significant disability/incapacity; resulted in a congenital anomaly/birth defect; or was an important medical event that could jeopardize the patient and required medical or surgical intervention to prevent any of the outcomes listed above. Serious AEs were followed by the investigator until resolution, until a medically acceptable outcome was reached, or until the patient was lost to follow-up.

7.3.1 Adverse Event Profile

The frequency of TEAEs and discontinuations due to TEAEs were roughly equivalent in the Dacogen and the cytarabine groups (Table 18). Rates of serious TEAEs and TEAEs requiring dose reduction were slightly higher in the Dacogen group compared with the cytarabine group.

Table 18 Safety Profile for Dacogen and Comparator Treatments, Study 016

	Patients, n (%)			
		Treatment Choice (TC)		
Adverse Event Parameter	**Dacogen N = 238**	**Total TC N = 237**	**Cytarabine N = 208**	**SC N = 29**
Any grade TEAE	237 (99.6)	231 (97.5)	208 (100.0)	23 (79.3)
Grade 3 – 4 TEAEs	220 (92.4)	202 (85.2)	186 (89.4)	16 (55.2)
Grade 3 – 5 TEAEs	226 (95.0)	208 (87.8)	191 (91.4)	17 (60.7)
Serious TEAEs[a]	194 (81.5)	163 (68.8)	151 (72.6)	12 (41.4)
TEAEs requiring dose intervention				
Discontinuation of treatment due to TEAE	98 (41.2)	100 (42.2)	97 (46.6)	3 (10.3)
TEAE(s) leading to dose delay	73 (30.7)	58 (24.5)	58 (27.9)	0
TEAE(s) leading to dose reduction	32 (13.4)	20 (8.4)	20 (9.6)	0
AEs with an outcome of death	70 (29.4)	59 (24.9)	55 (26.4)	4 (13.8)

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.
a: Incidence of serious AEs on this table includes deaths.
Source: ISS Tables 4.1.1, 4.3.1.1, and 6.4; SCS Table 9, pg 35

7.3.2 Commonly Reported Treatment-Emergent Adverse Events

The incidence of TEAEs was similar in the Dacogen (99.6%) and TC (97.5%) arms. Overall, the most common TEAEs were hematologic and those related to infections. Table 19 displays all TEAEs regardless of causality that were reported by at least 10% of patients in either study arm. When viewing the hematologic AE data, it is important to bear in mind that cytopenias are typical of the natural course of AML. Especially for patients receiving SC, cytopenias may

not have been considered and reported as AEs by the investigator. Hematologic parameters based on laboratory values are presented in Table 21.

Table 19 Common Treatment-Emergent Adverse Events Reported in ≥ 10% of Patients (Study 016 Safety Population)

		Treatment Choice (TC)		
Preferred Term[a]	**Dacogen N = 238**	**Total TC N = 237**	**Cytarabine N = 208**	**SC N = 29**
Patients with ≥ 1 AE, n (%)	**237 (99.6)**	**231 (97.5)**	**208 (100.0)**	**23 (79.3)**
Pyrexia	116 (48.7)	88 (37.1)	82 (39.4)	6 (20.7)
Thrombocytopenia	107 (45.0)	87 (36.7)	83 (39.9)	4 (13.8)
Anemia	98 (41.2)	74 (31.2)	70 (33.7)	4 (13.8)
Febrile neutropenia	82 (34.5)	55 (23.2)	55 (26.4)	0
Neutropenia	79 (33.2)	49 (20.7)	48 (23.1)	1 (3.4)
Diarrhea	70 (29.4)	55 (23.2)	50 (24.0)	5 (17.2)
Nausea	67 (28.2)	69 (29.1)	64 (30.8)	5 (17.2)
Hypokalemia	64 (26.9)	44 (18.6)	39 (18.8)	5 (17.2)
Pneumonia	60 (25.2)	51 (21.5)	46 (22.1)	5 (17.2)
Constipation	56 (23.5)	38 (16.0)	36 (17.3)	2 (6.9)
Disease progression	55 (23.1)	59 (24.9)	56 (26.9)	3 (10.3)
Leukopenia	53 (22.3)	26 (11.0)	26 (12.5)	0
Cough	52 (21.8)	40 (16.9)	37 (17.8)	3 (10.3)
Edema peripheral	52 (21.8)	43 (18.1)	41 (19.7)	2 (6.9)
Asthenia	45 (18.9)	30 (12.7)	28 (13.5)	2 (6.9)
Dyspnea	45 (18.9)	44 (18.6)	38 (18.3)	6 (20.7)
Hypoalbuminemia	41 (17.2)	23 (9.7)	21 (10.1)	2 (6.9)
Epistaxis	39 (16.4)	36 (15.2)	34 (16.3)	2 (6.9)
General physical health deterioration	38 (16.0)	42 (17.7)	37 (17.8)	5 (17.2)
Hypocalcemia	37 (15.5)	19 (8.0)	16 (7.7)	3 (10.3)
Vomiting	37 (15.5)	35 (14.8)	32 (15.4)	3 (10.3)
Urinary tract infection	37 (15.5)	14 (5.9)	13 (6.3)	1 (3.4)
Abdominal pain	36 (15.1)	13 (5.5)	13 (6.3)	0
Fatigue	34 (14.3)	31 (13.1)	28 (13.5)	3 (10.3)
Hyperglycemia	33 (13.9)	18 (7.6)	16 (7.7)	2 (6.9)
Hepatic function abnormal	33 (13.9)	23 (9.7)	22 (10.6)	1 (3.4)
Headache	33 (13.9)	27 (11.4)	26 (12.5)	1 (3.4)
Hyponatremia	28 (11.8)	10 (4.2)	9 (4.3)	1 (3.4)
Insomnia	26 (10.9)	25 (10.5)	22 (10.6)	3 (10.3)
Anorexia	25 (10.5)	24 (10.1)	21 (10.1)	3 (10.3)
Pain in extremity	25 (10.5)	11 (4.6)	11 (5.3)	0
Petechiae	25 (10.5)	16 (6.8)	16 (7.7)	0
Dizziness	17 (7.1)	25 (10.5)	23 (11.1)	2 (6.9)

Abbreviations: AE = adverse event; SC = supportive care and palliative measures; TC = patient's choice of treatment with the advice of their physician.
a: Table includes AEs of any grade (Grade 1 to 5). A patient with multiple occurrences of an AE is counted only once at the maximum grade at which the event occurred; only treatment-emergent events are included.
Source: SCS Table 10. Appendix Table 6 and ISS Table 4.2

The incidence of Grade ≥ 3 TEAEs showed a numerical increase for some parameters in the Dacogen arm compared with the TC arm in Study 016 (Table 20). The most common Grade ≥ 3 TEAEs were febrile neutropenia, anemia, pneumonia, hypokalemia, and thrombocytopenia.

As noted previously, patients in the Dacogen arm were observed for safety nearly twice as long as patients in the TC arm. In the context of AML and the longer treatment period in the Dacogen arm, the observed differences do not appear clinically substantive. This is discussed further with respect to hematologic laboratory parameters below.

Table 20 Grade ≥ 3 Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients, Study 016

	Patients, n (%)			
		Treatment Choice (TC)		
Preferred Term[a]	**Dacogen[b] N = 238**	**Total TC[b] N = 237**	**Cytarabine[b] N = 208**	**SC[b] N = 29**
Patients with at least 1 Grade ≥ 3 AE	226 (95)	208 (88)	191 (92)	17 (59)
Thrombocytopenia	97 (41)	77 (32)	73 (35)	4 (14)
Anemia	82 (34)	61 (26)	57 (27)	4 (14)
Febrile neutropenia	79 (33)	51 (22)	51 (25)	0
Neutropenia	77 (32)	45 (19)	44 (21)	1 (3)
Pneumonia	53 (22)	43 (18)	39 (19)	4 (14)
Disease progression	50 (21)	56 (24)	53 (25)	3 (10)
Leukopenia	47 (20)	20 (8)	20 (10)	0
General physical health deterioration	30 (13)	37 (16)	32 (15)	5 (17)
Hypokalemia	28 (12)	24 (10)	19 (9)	5 (17)
Pyrexia	24 (10)	20 (8)	17 (8)	3 (10)
Sepsis	18 (8)	10 (4)	9 (4)	1 (3)
Dyspnea	16 (7)	14 (6)	11 (5)	3 (10)
Urinary tract infection	16 (7)	6 (3)	5 (2)	1 (3)
Septic shock	17 (7)	8 (3)	8 (4)	0
Hyponatremia	12 (5)	4 (2)	4 (2)	0
Hypoalbuminemia	11 (5)	2 (1)	2 (1)	0
Asthenia	12 (5)	9 (4)	8 (4)	1 (3)
Atrial fibrillation	9 (4)	11 (5)	9 (4)	2 (7)
Bronchopneumonia	10 (4)	14 (6)	11 (5)	3 (10)
Fatigue	5 (2)	6 (3)	6 (3)	0
Leukocytosis	5 (2)	11 (5)	11 (5)	0

Abbreviations: AE = adverse event; SC = supportive care and palliative measures; TC = patient's choice of treatment with the advice of their physician.
a: Table includes the incidence of patients who had an AE with a maximum (worst) grade of 3, 4, or 5.
b: A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum grade experienced. Only treatment-emergent events are included.
Source: Source table provided 10-08-11 (Output dae01-gradege3)

Multilineage cytopenias are a hallmark of AML and reflect the natural history of the disease. Therefore, assessing hematologic parameters solely according to the definitions for TEAEs does not provide a complete clinical picture and the clinical laboratory data need to be evaluated. Indeed, baseline laboratory values show that the majority of patients had cytopenias at study entry. The incidence of Grade 3 or 4 cytopenias, as derived from the laboratory data, at baseline and on study treatment are shown in Table 21. This display of the data shows that Grade 3 and 4 myelosuppression was numerically more common in the Dacogen arm compared with the TC arm, but the differences are not clinically significant in the context of AML. The increased incidence of Grade 3 or 4 myelosuppression in the Dacogen arm may also reflect the longer treatment period in the Dacogen arm.

Table 21 Worst CTCAE Grade 3 or 4 Hematologic Toxicity at Baseline and During Study Treatment Based on Laboratory Values

	Patients, n (%)							
			Treatment Choice (TC)					
	Dacogen		Total TC		Cytarabine		SC	
Preferred Term	N = 238		N = 237		N = 208		N = 29	
	Baseline	On-study	Baseline	On-study	Baseline	On-study	Baseline	On-study
Anemia	37 (15.5)	129 (54.2)	30 (12.7)	102 (43.0)	25 (12.0)	89 (42.8)	5 (17.2)	13 (44.8)
Neutropenia	137 (57.6)	194 (81.5)	138 (58.2)	162 (68.4)	124 (59.6)	149 (71.6)	14 (48.3)	13 (44.8)
Thrombocytopenia	101 (42.4)	195 (81.9)	103 (43.5)	189 (79.7)	87 (41.8)	169 (81.3)	16 (55.2)	20 (69.0)
WBC	70 (29.4)	169 (71.0)	72 (30.4)	122 (51.5)	66 (31.7)	113 (54.3)	6 (20.7)	9 (31.0)

CTCAE = Common Terminology Criteria for Adverse Events; SC = supportive care, TC = patient's choice of treatment with physician's advice; WBC = white blood cell count.
Clinical Study Report Addendum, clinical cutoff 29 October 2010.
Source: dlab-g34.rtf generated by dlab-g34.sas

7.3.3 Safety Profile by Cycle

Given the longer duration of treatment with Dacogen in Study 016, examination of AEs by cycle may provide a better assessment of whether toxicity associated with Dacogen was comparable to toxicity associated with low-dose cytarabine. In the first two cycles of study treatment, the incidence of AEs was comparable between the Dacogen and TC arms (Table 22). Moreover, the safety profile of Dacogen did not worsen over time with continued therapy.

Table 22 Treatment-Emergent Adverse Events for Selected System Organ Classes by Cycle, Study 016 (Safety Population)

MedDRA SOC	Patients, n (%)					
Treatment Arm	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5/6	Cycle 7/8
Blood and Lymphatic System[a]						
Dacogen	130 (54.6)	87 (46.8)	71 (45.8)	54 (40.0)	57 (51.4)	47 (51.6)
Total TC[b]	113 (47.7)	79 (47.0)	49 (45.0)	33 (37.1)	27 (38.6)	18 (40.0)
Cardiac Disorders						
Dacogen	28 (11.8)	11 (5.9)	8 (5.2)	9 (6.7)	4 (3.6)	5 (5.5)
Total TC[b]	32 (13.5)	17 (10.1)	3 (2.8)	3 (3.4)	5 (7.1)	2 (4.4)
Infections and Infestations						
Dacogen	91 (38.2)	58 (31.2)	41 (26.5)	29 (21.5)	32 (28.8)	31 (34.1)
Total TC[b]	80 (33.8)	40 (23.8)	21 (19.3)	13 (14.6)	14 (20.0)	10 (22.2)
Nervous System Disorders						
Dacogen	36 (15.1)	16 (8.6)	17 (11.0)	9 (6.7)	8 (7.2)	14 (15.4)
Total TC[b]	34 (14.3)	23 (13.7)	10 (9.2)	7 (7.9)	5 (7.1)	5 (11.1)
Renal and Urinary Disorders						
Dacogen	23 (9.7)	13 (7.0)	11 (7.1)	3 (2.2)	10 (9.0)	6 (6.6)
Total TC[b]	18 (7.6)	14 (8.3)	5 (4.6)	3 (3.4)	5 (7.1)	2 (4.4)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TC = treatment choice.
a: SOC of *Blood and Lymphatic Disorders* includes events other than myelosuppression.
b: Includes supportive care and cytarabine treatments.
Source: SCS Table 15, pg 47; ISS Tables 4.2, 4.5.1, 4.5.2, 4.5.4 and 4.5.6

Assessment of absolute neutrophil counts (ANC) by cycle is shown in Table 23. This table shows the proportion of patients with laboratory values consistent with Grade 3 or 4 neutropenia, based on NCI Common Terminology Criteria for Adverse Events criteria (v 3.0), at baseline, on Day 1 of each cycle, and at the nadir for each cycle. The percentage is based on the total number of patients assessed at each cycle. Approximately 60% of patients had Grade 3 or 4 neutropenia at baseline. There was a somewhat higher numerical incidence of neutropenia in the Dacogen arm compared with the TC arm, but these differences are unlikely to be clinically meaningful in the context of this disease. There was no dramatic change from baseline in either group. Among patients in the TC arm receiving supportive care, although few samples were drawn, all evaluable patients who remained on study became neutropenic by Cycle 5. This reflects the natural history of the disease.

Table 23 Grade 3 and 4 Neutropenia Based on Laboratory Values

		Patients, n/N (%)			
			Treatment Choice (TC)		
		Dacogen N = 238	Total TC N = 237	Cytarabine N = 208	SC N = 29
Baseline		137/223 (61.4)	138/228 (60.5)	124/202 (61.4)	14/26 (53.8)
Cycle 1	Day 1	54/103 (52.4)	51/97 (52.6)	51/93 (54.8)	0/4 (0)
	Nadir	156/226 (69.0)	139/217 (64.1)	129/194 (66.5)	10/23 (43.5)
Cycle 2	Day 1	97/156 (62.2)	73/127 (57.5)	69/122 (56.6)	4/5 (80.0)
	Nadir	134/180 (74.4)	110/166 (66.3)	102/150 (68.0)	8/16 (50.0)
Cycle 3	Day 1	81/137 (59.1)	44/85 (51.8)	41/81 (50.6)	3/4 (75.0)
	Nadir	109/153 (71.2)	60/106 (56.6)	55/94 (58.5)	5/12 (41.7)
Cycle 4	Day 1	67/115 (58.3)	33/73 (45.2)	31/69 (44.9)	2/4 (50.0)
	Nadir	94/134 (70.1)	45/89 (50.6)	40/77 (51.9)	5/12 (41.7)
Cycle 5	Day 1	60/93 (64.5)	28/58 (48.3)	26/56 (46.4)	2/2 (100)
	Nadir	77/110 (70.0)	36/69 (52.2)	32/63 (50.8)	4/6 (66.7)
Cycle 6	Day 1	41/85 (48.2)	23/49 (46.9)	20/46 (43.5)	3/3 (100)
	Nadir	67/98 (68.4)	28/55 (50.9)	23/50 (46.0)	5/5 (100)
Cycle 7	Day 1	45/79 (57.0)	18/39 (46.2)	14/35 (40.0)	4/4 (100)
	Nadir	63/90 (70.0)	22/43 (51.2)	17/38 (44.7)	5/5 (100)
Cycle 8	Day 1	34/68 (50.0)	11/34 (32.4)	10/33 (30.3)	1/1 (100)
	Nadir	54/79 (68.4)	16/39 (41.0)	14/37 (37.8)	2/2 (100)

Abbreviations: TC = treatment choice; SC = supportive care.
Clinical Study Report Addendum, clinical cutoff 29 October 2010.
Source: dlab-g34-2.rtf generated by dlab-g34-2.sas

7.4 Deaths, Serious Adverse Events, Adverse Events Causing Discontinuations, and Adverse Events Requiring Treatment Modifications

The overall incidence of on-treatment deaths due to disease progression or other AE and the incidence of early deaths (i.e., within 30 days of first study treatment) were similar in the Dacogen and TC arms (Table 24). The incidence of early deaths was low in both arms (8.8% and 8.0% in the Dacogen and TC arms, respectively). Infections led to death in 10.9% and 10.1% of patients in the Dacogen and TC arms, respectively, and most often were attributed to pneumonia, bronchopneumonia, sepsis, or septic shock. Adverse events led to death in a higher percentage of patients receiving Dacogen compared with TC. However, there did not appear to be any relevant differences between Dacogen and cytarabine either in the type or frequency of AEs with an outcome of death after accounting for the longer duration of Dacogen treatment and the longer observation period for safety.

Table 24 Overview of On-Treatment Deaths (Safety Population)

Preferred Term[a]	Patients, n (%)			
		Treatment choice (TC)		
	Dacogen N = 238	Total TC[a] N = 237	Cytarabine N = 208	SC N = 29
On-treatment deaths				
AEs with an outcome of death[c]	70 (29.4)	59 (24.9)	55 (26.4%)	4 (13.8)
Disease progression	14 (5.9)	16 (6.8)	15 (7.2)	1 (3.4)
Other AE leading to death	59 (24.8)	48 (20.3)	44 (21.2)	4 (13.8)
Deaths within 30 days of first dose[d,e,]	21 (8.8)	19 (8.0)	17 (8.2)	2 (6.9)
Deaths within 30 days of last dose[e]	69 (29.0)	58 (24.5)	54 (26.0)	4 (13.8)

Abbreviations: AE = adverse event; CRF = case report form; SC = supportive care and palliative measures; TC = patient's choice of treatment with the advice of their physician.

Observation period extends beyond 56 days posttreatment. All events are treatment emergent.

a: Includes SC and cytarabine treatments.

b: If both disease progression and AE were listed as the cause of death, disease progression was reported on the Death page of the CRF.

c: If both disease progression and AE were listed as the cause of death, the patient would be counted in both categories.

d: Within 30 days of randomization for patients who received SC.

e: Deaths within 30 days of first dose and within 30 days of last dose are not mutually exclusive categories.

Source: ISS Tables 6.1.1 and 6.4; SCS Table 16, p 49

7.4.1 Adverse Events Resulting in Death

In Study 016, 29.4% and 24.9% of patients in the Dacogen and TC arms, respectively, had an AE with an outcome of death during the observation period (Table 25). Disease progression was the most frequently reported cause of death in both arms followed by septic shock, pneumonia, and sepsis.

Table 25 Adverse Events in Two or More Patients in Any Treatment Arm with an Outcome of Death During the Observation Period (Safety Population)

	Patients, n (%)			
		Treatment Choice (TC)		
Preferred Term	**Dacogen N = 238**	**Total TC N = 237**	**Cytarabine N = 208**	**SC N = 29**
AE with outcome of death	70 (29.4)	59 (24.9)	55 (26.4)	4 (13.8)
Disease progression	14 (5.9)	16 (6.8)	15 (7.2)	1 (3.4)
Septic shock	12 (5.0)	7 (3.0)	7 (3.4)	0
Pneumonia	6 (2.5)	9 (3.8)	8 (3.8)	1 (3.4)
Sepsis	6 (2.5)	3 (1.3)	3 (1.4)	0
Cardiac arrest	5 (2.1)	3 (1.3)	3 (1.4)	0
Multi-organ failure	5 (2.1)	3 (1.3)	3 (1.4)	
Cardiac failure	3 (1.3)	0	0	0
Hemorrhage intracranial	3 (1.3)	1 (0.4)	1 (0.5)	0
Acute respiratory failure	3 (1.3)	1 (0.4)	1 (0.5)	0
Bronchopneumonia	2 (0.8)	6 (2.5)	5 (2.4)	1 (3.4)
Disseminated intravascular coagulation	2 (0.8)	0	0	0
Cerebral hemorrhage	2 (0.8)	0	0	0
Acute pulmonary edema	2 (0.8)	0	0	0
Respiratory failure	1 (0.4)	3 (1.3)	2 (1.0)	1 (3.4)
General physical health deterioration	0	2 (0.8)	2 (1.0)	0
Pulmonary edema	0	4 (1.7)	3 (1.4)	1 (3.4)

Abbreviations: AE = adverse event; SC = supportive care and palliative measures; TC = patient's choice of treatment with the advice of their physician.

Source: SCS Table 18 pg 55-56

7.4.2 Serious Adverse Events

The most prevalent SAEs observed were disorders of the blood and lymphatic system and infections (i.e., cytopenias, febrile neutropenia, and pneumonia), as shown in Table 26. Cytopenias and infections are frequent manifestations of AML, and are also expected side effects of cytarabine and Dacogen treatment. They are generally manageable as part of routine medical care given by oncologists. The overall percentage of patients with an SAE was similar in both arms, particularly when taking into account the longer safety observation period in the Dacogen arm. Specific SAEs that occurred at a higher frequency in the Dacogen arm compared with the TC arm were febrile neutropenia, pneumonia, thrombocytopenia, neutropenia, and septic shock.

Table 26 Nonfatal Serious Adverse Events in ≥ 5% of Patients in Any Treatment Arm (Safety Population)

		Treatment Choice (TC)		
Preferred Term[a]	**Dacogen N = 238**	**Total TC N = 237**	**Cytarabine N = 208**	**SC N = 29**
Patients with ≥ 1 SAE, n (%)	185 (77.7)	156 (65.8)	145 (69.7)	11 (37.9)
Febrile neutropenia	61 (25.6)	34 (14.3)	34 (16.3)	0
Pneumonia	50 (21.0)	36 (15.2)	33 (15.9)	3 (10.3)
Pyrexia	23 (9.7)	20 (8.4)	18 (8.7)	2 (6.9)
Thrombocytopenia	21 (8.8)	11 (4.6)	11 (5.3)	0
Disease progression	20 (8.4)	19 (8.0)	18 (8.7)	1 (3.4)
General physical health deterioration	16 (6.7)	13 (5.5)	12 (5.8)	1 (3.4)
Anemia	15 (6.3)	12 (5.1)	12 (5.8)	0
Neutropenia	15 (6.3)	7 (3.0)	7 (3.4)	0
Sepsis	15 (6.3)	9 (3.8)	8 (3.8)	1 (3.4)
Septic shock	12 (5.0)	5 (2.1)	5 (2.4)	0
Bronchopneumonia	9 (3.8)	11 (4.6)	8 (3.8)	3 (10.3)
Atrial fibrillation	4 (1.7)	10 (4.2)	8 (3.8)	2 (6.9)

Abbreviations: SAE = adverse event; SC = supportive care and palliative measures; TC = patient's choice of treatment with the advice of their physician.
A patient with multiple occurrences of an SAE is counted only once in the AE category at the maximum grade experienced.
Table excludes Grade 5 SAEs, but does include Grade 1-4 events with an outcome of death.
a: Only treatment-emergent events are included.
Source: SCS Table 19 pg 58; Appendix Table 15 and ISS Table 7.1.1

An analysis of treatment-emergent SAEs occurring in the first 30 days on study was conducted to control for the difference in duration of treatment between arms. This analysis showed that there were no meaningful differences in the incidence of SAEs between the Dacogen and TC arms during Cycle 1 (Table 27).

Table 27 Treatment-Emergent SAEs Occurring in the First 30 Days in > 2 Patients in Any Treatment Group, Study 016 (Safety Population)

		Patients, n (%)		
	Dacogen (N = 238)	**Total TC**[a] **(N = 237)**	**Cytarabine (N = 208)**	**SC (N = 29)**
Febrile neutropenia	23 (10)	18 (8)	18 (9)	0
Pneumonia	19 (8)	17 (7)	15 (7)	2 (7)
Pyrexia	11 (5)	9 (4)	8 (4)	1 (3)
Thrombocytopenia	8 (3)	7 (3)	7 (3)	0
Sepsis	6 (3)	3 (1)	3 (1)	0
Urinary tract infection	6 (3)	2 (1)	2 (1)	0
Anemia	5 (2)	4 (2)	4 (2)	0

		Patients, n (%)		
	Dacogen (N = 238)	Total TC[a] (N = 237)	Cytarabine (N = 208)	SC (N = 29)
Neutropenia	4 (2)	3 (1)	3 (1)	0
Bronchopneumonia	4 (2)	2 (1)	2 (1)	0
Bacteremia	3 (1)	1 (<1)	1 (<1)	0
Lobar pneumonia	3 (1)	1 (<1)	1 (<1)	0
Septic shock	3 (1)	1 (<1)	1 (<1)	0
Staphylococcal infection	3 (1)	1 (<1)	1 (<1)	0
Acute respiratory distress syndrome	3 (1)	0	0	0
Renal impairment	3 (1)	1 (<1)	1 (<1)	0
General physical health deterioration	2 (1)	4 (2)	4 (2)	0
Cardiac failure	1 (<1)	3 (1)	2 (1)	1 (3)
Diarrhea	1 (<1)	3 (1)	3 (1)	0

Abbreviations: SC = supportive care and palliative measures; TC = treatment choice.
a: Includes SC and cytarabine treatments.
Source: dae09-nf30.

7.4.3 Discontinuations, Dose Delays, and Dose Reductions Due to Adverse Events

Table 28 shows the distribution of patients in Study 016 who had dose discontinuations, delays, reductions, or interruptions. No distinct differences between treatment arms were evident in the data. Adverse events that most frequently led to permanent discontinuation of study treatment were deterioration of general physical health and disease progression. No other single AE occurred in > 3% of patients in either arm. There were no significant differences in the overall incidence of discontinuation due to AEs between Dacogen and cytarabine arms.

A similar percentage of patients in the Dacogen and cytarabine arms had a dose delay due to an AE. Dacogen was most frequently delayed (≥ 5% of patients) due to neutropenia, pneumonia, and febrile neutropenia. The majority of other AEs that led to a delay of study treatment were fewer than 1% of patients with either treatment arm.

The percentage of patients who had a dose reduction due to an AE was slightly higher in the Dacogen arm than in the TC arm, most likely due to the longer duration of treatment in the Dacogen arm. The only AEs that led to dose reduction in > 1% of Dacogen-treated patients were decreased weight and hepatic function abnormal. Conversely, the only AEs that led to dose reduction in > 1% of cytarabine-treated patients were hematologic in nature and included neutropenia, anemia, and thrombocytopenia.

The percentage of patients who had a dose interruption due to an AE was similar in the Dacogen and cytarabine arms. The AEs that most frequently led to dose interruption in both arms were febrile neutropenia, pyrexia, and pneumonia.

Table 28 Incidence of Patients Who Had a Dosing Intervention Due to an Adverse Event (Safety Population)

	Patients, n (%)			
		Treatment Choice (TC)		
Preferred Term	Dacogen N = 238	Total TC[a] N = 237	Cytarabine N = 208	SC N = 29
Dose intervention of permanent discontinuation, dose delay,[b] or dose reduction only[c]	163 (68.5)	153 (64.6)	149 (71.6)	4 (13.8)
Permanent discontinuation	98 (41.2)	100 (42.2)	97 (46.6)	3 (10.3)
Dose delay[b]	73 (30.7)	58 (24.5)	58 (27.9)	0
Dose reduction	32 (13.4)	20 (8.4)	20 (9.6)	0
Dose interruption	30 (12.6)	27 (11.4)	27 (13.0)	0

Information for this table was obtained from the AE page in the CRF

Abbreviations: SC = supportive care and palliative measures; TC = patient's choice of treatment with the advice of their physician.

a: Includes SC and cytarabine treatments.

b: Includes delay of any dose, not just the first dose of the cycle.

c: Patients may have had more than one type of dose intervention.

Source: ISS Table 8.1; SCS Table 21, p 62

7.5 Special Safety Topics

Based on the known characteristics of AML and the safety profile of Dacogen previously established in patients with MDS, the AEs of special interest are hematologic events (e.g., thrombocytopenia, febrile neutropenia, neutropenia, anemia), bleeding events, and infections. Gastrointestinal events were also reported frequently in the Dacogen arms, but the vast majority of these were mild or moderate (Grade 1 or 2) in severity.

7.5.1 Myelosuppression

Due to the nature of AML, many patients had abnormalities in baseline laboratory values for one or more hematologic parameters, including WBC count, ANC, hemoglobin, and platelets. Myelosuppression is a consequence of AML, but may also occur as a result of drug treatment. Table 29 presents Grade 3 or 4 neutropenia and thrombocytopenia based on laboratory values and myelosuppression events reported as AEs. Myelosuppression is a broad MedDRA term that encompasses more than 100 different terms, including the key hematologic parameters of WBC count, ANC, hemoglobin, and platelets. The incidence of Grade 3 or 4 cytopenias, as derived from the laboratory data, shows that Grade 3 and 4 myelosuppression was numerically more common in the Dacogen arm compared with the TC arm, but the differences are not clinically significant in the context of AML. Rates of treatment discontinuation due to myelosuppression AEs (3.4% and 5.1% for Dacogen and TC arms, respectively) and deaths due to myelosuppression AEs (1.7% and 0.4% for Dacogen and TC arms, respectively) were low in both arms, suggesting that investigators could manage myelosuppression and continue

therapy. These results were likely affected by the longer treatment and safety reporting period for patients in the Dacogen arm, as discussed previously in Section 7.3.

Table 29 Myelosuppression Profile, Study 016 (Safety Population)

		Patients, n (%)		
	Dacogen (N = 238)	Total TC[b] (N = 237)	Cytarabine (N = 208)	SC (N = 29)
Any myelosuppression AE	177 (74.4)	146 (61.6)	138 (66.3)	8 (27.6)
Grade 3 or 4 neutropenia[a]	194 (81.5)	162 (68.4)	149 (71.6)	13 (44.8)
Grade 3 or 4 thrombocytopenia[a]	195 (81.9)	189 (79.7)	169 (81.3)	20 (69.0)
Myelosuppression AE reported as treatment related[c]	119 (50.0)	102 (43.0)	102 (49.0)	0
Serious myelosuppression event	86 (36.1)	59 (24.9)	59 (28.4)	0
Hospitalized for myelosuppression	79 (33.2)	52 (21.9)	52 (25.0)	0
Treatment discontinuation for myelosuppression event	8 (3.4)	12 (5.1)	12 (5.8)	0
Death attributed to myelosuppression event[d]	4 (1.7)	1 (0.4)	1 (0.5)	0

Abbreviations: AE = adverse event; SC, supportive care and palliative measures; TC = treatment choice.
a: Derived from laboratory values (see Table 21).
b: Includes SC and cytarabine treatments.
c: Investigator-assessed causality.
d: Death that occurred any time throughout the study.
Source: Table 5.1 (9/22)

7.5.2 Infection

The most frequently reported infections were pneumonia, sepsis, and urinary tract infection (Table 30). The overall incidence of infections was similar in the Dacogen and TC arms after accounting for different durations of treatment.

Laboratory data show that mean nadir values for neutrophils, lymphocytes, and WBC were lower with Dacogen in later cycles compared with the TC arm; however, infections tended to occur early in treatment and did not increase in frequency over subsequent cycles of treatment. Thus, there did not appear to be delayed or cumulative toxicity over time with Dacogen. These results suggest that Dacogen does not produce an increased risk of infection over prolonged treatment.

Table 30 Infections: Adverse Event Profile, Study 016 (Safety Population)

		Treatment Choice (TC)		
Patients With Infection AE, n (%)	Dacogen N = 238	Total TC[a] N = 237	Cytarabine N = 208	SC N = 29
Any infection[b]	199 (83.6)	160 (67.5)	148 (71.2)	12 (41.4)
Grade 3 or 4 infection	142 (59.7)	109 (46.0)	101 (48.6)	8 (27.6)
Infections reported as treatment-related[c]	88 (37.0)	65 (27.4)	64 (30.8)	1 (3.4)
Serious infection	137 (57.6)	98 (41.4)	90 (43.3)	8 (27.6)

Patients With Infection AE, n (%)	Dacogen N = 238	Treatment Choice (TC) Total TC[a] N = 237	Cytarabine N = 208	SC N = 29
Hospitalized for infection	130 (54.6)	84 (35.4)	78 (37.5)	6 (20.7)
Treatment discontinuation for infection	22 (9.2)	18 (7.6)	16 (7.7)	2 (6.9)
Death attributed to infection	27 (11.3)	24 (10.1)	22 (10.6)	2 (6.9)

Abbreviations: AE = adverse event; SC = supportive care and palliative measures; TC = treatment choice.
a: Includes SC and cytarabine treatments.
b: A patient with multiple occurrences of an AE was counted only once in the AE category at the maximum grade.
c: Investigator-assessed causality.
Source: ISS Table 5.2; SCS Table 28, p 74

7.5.3 Bleeding Events

Bleeding events were reported in a similar percentage of patients receiving Dacogen or TC despite the longer treatment duration with Dacogen (Table 31). The most frequently reported bleeding events, occurring in ≥ 5% of patients in either arm, were epistaxis, petechiae, contusion, gingival bleeding, and hematoma. In general, these were similar in type and frequency between treatment arms, and the vast majority of bleeding events were Grade 1 or 2 in severity.

Table 31 Bleeding Events: Adverse Event Profile, Study 016 (Safety Population)

Patients With Bleeding Event AE, n (%)	Dacogen N = 238	Treatment Choice (TC) Total TC[a] N = 237	Cytarabine N = 208	SC N = 29
Any bleeding event	107 (45.0)	102 (43.0)	95 (45.7)	7 (24.1)
Grade 3 or 4 bleeding event	20 (8.4)	22 (9.3)	20 (9.6)	2 (6.9)
Bleeding events reported as treatment related[b]	27 (11.3)	30 (12.7)	30 (14.4)	0
Serious bleeding event	21 (8.8)	19 (8.0)	18 (8.7)	1 (3.4)
Hospitalized for bleeding event	15 (6.3)	18 (7.6)	17 (8.2)	1 (3.4)
Treatment discontinuation for bleeding event	2 (0.8)	4 (1.7)	4 (1.9)	0
Death attributed to bleeding event	4 (1.7)	4 (1.7)	4 (1.9)	0

Abbreviations: AE = adverse event; SC = supportive care and palliative measures; TC = treatment choice.
a: Includes SC and cytarabine treatments.
b: Investigator-assessed causality.
Source: ISS Table 5.4; SCS Table 31, p 78

7.5.4 Renal Toxicity

Approximately 20% of patients in each treatment arm had a renal AE. Although the overall incidence of renal AEs was similar across treatment arms, Dacogen-treated patients were more likely to have a serious renal event, most likely due to the longer safety observation period compared with the TC arm (Table 32). The only renal AE that occurred in ≥ 5% of patients in either treatment arm was renal impairment (Table 19).

Table 32 Renal Events: Adverse Event Profile, Study 016 (Safety Population)

Patients With Renal Event AE, n (%)	Dacogen N = 238	Treatment Choice (TC) Total TC[a] N = 237	Cytarabine N = 208	SC N = 29
Any renal event	58 (24.4)	47 (19.8)	42 (20.2)	5 (17.2)
Grade 3 or 4 renal AE	18 (7.6)	13 (5.5)	11 (5.3)	2 (6.9)
Renal events reported as treatment related[b]	7 (2.9)	9 (3.8)	9 (4.3)	0
Serious renal AE	14 (5.9)	7 (3.0)	6 (2.9)	1 (3.4)
Treatment discontinuation for renal AE	1 (0.4)	1 (0.4)	1 (0.5)	0
Death attributed to renal AE	0	1 (0.4)	1 (0.5)	0

Abbreviations: AE = adverse event; SC = supportive care and palliative measures; TC = treatment choice.
a: Includes SC and cytarabine treatments.
b: Investigator-assessed causality.
Source: ISS Tables 4.3.2, 4.3.3, 4.4, 5.8.1, 5.8.2, 6.1.1, 6.2, 7.1.1 and 8.3; SCS Table 40, pg 92

7.5.5 Cardiac Events

The incidence and severity of cardiac events observed in Study 016 were consistent with the known incidence of cardiac events in the elderly population, given the prevalence of pre-existing cardiac disease and expected rate of new cardiac events over time in this population. There were no notable differences in the cardiac safety profile between treatment arms, and no increase in cardiac events was observed over the treatment period in either arm (Table 33).

Table 33 Cardiac Events: Adverse Event Profile, Study 016 (Safety Population)

Patients With Cardiac Event AE, n (%)	Dacogen N = 238	Treatment Choice (TC) Total TC[a] N = 237	Cytarabine N = 208	SC N = 29
Any cardiac AE	70 (29.4)	63 (26.6)	57 (27.4)	6 (20.7)
Grade 3 or 4 cardiac AE	28 (11.8)	24 (10.1)	21 (10.1)	3 (10.3)
Cardiac AEs reported as treatment related[b]	7 (2.9)	5 (2.1)	5 (2.4)	0
Serious cardiac AE	22 (9.2)	19 (8.0)	17 (8.2)	2 (6.9)
Treatment discontinuation for cardiac AE	7 (2.9)	4 (1.7)	4 (1.9)	0
Death attributed to cardiac AE	13 (5.5)	6 (2.5)	6 (2.9)	0

Abbreviations: AE = adverse event; SC = supportive care and palliative measures; TC = treatment choice.
a: Includes SC and cytarabine treatments.
b: Investigator-assessed causality.
Source: ISS Tables 4.3.2, 4.3.3, 4.4, 5.6.1, 5.6.2, 6.1.1, 6.2, 7.1.1 and 8.3; SCS Table 34, p 83

The higher percentage of cardiac-related deaths among Dacogen-treated patients may be attributed to several factors.

- Patients in the Dacogen arm had a longer treatment duration and safety observation period compared with TC arm.

- Nearly half of the cardiac-related deaths in the Dacogen arm were reported at one site in Eastern Europe.
- Some deaths of unknown cause were reported with a verbatim term of "cardiac arrest," which coded to the Cardiac Disorders SOC.

A complete listing of all patients in both Studies (Study 016 and Study 017) with fatal cardiac-related AEs is provided in Appendix Table 38.

7.5.6 Central Nervous System Events

In Study 016, the most frequently reported central nervous system (CNS) events, occurring in ≥ 10% of patients, were headache and dizziness (Table 19). These occurred with similar frequency in both treatment arms, and the majority of CNS events were Grade 1 or 2 in severity. The CNS safety profile of Dacogen was similar to that of TC, except for a higher incidence of CNS-related deaths in the Dacogen arm (Table 34). Seven CNS-related deaths occurred in the Dacogen arm compared with 2 in the TC arm, and many of those deaths were attributed to hemorrhage. The majority of CNS hemorrhages in both treatment arms occurred in patients with low platelet counts, and most of those patients had low platelet counts at baseline. A complete listing of all patients in both Studies (Study 016 and Study 017) with fatal CNS-related AEs is provided in Appendix Table 39.

Table 34 CNS Events: Adverse Event Profile, Study 016 (Safety Population)

		Treatment Choice (TC)		
Patients With CNS AEs, n (%)	**Dacogen N = 238**	**Total TC[a] N = 237**	**Cytarabine N = 208**	**SC N = 29**
Any CNS AE	82 (34.5)	73 (30.8)	67 (32.2)	6 (20.7)
Grade 3 or 4 CNS AE	19 (8.0)	16 (6.8)	16 (7.7)	0
CNS AE reported as treatment related[b]	16 (6.7)	19 (8.0)	19 (9.1)	0
Serious nonfatal CNS AEs	15 (6.3)	12 (5.1)	12 (5.8)	0
Serious nonfatal treatment-related CNS AEs	3 (1.3)	2 (0.8)	2 (1.0)	0
Treatment discontinuation for CNS AE	5 (2.1)	1 (0.4)	1 (0.5)	0
Death attributed to CNS AE[c]	7 (2.9)	2 (0.8)	2 (1.0)	0

Abbreviations: AE = adverse event; CNS = central nervous system; SC = supportive care and palliative measures; TC = patient's choice of treatment with the advice of their physician.

a: Includes SC and cytarabine treatments.

b: Investigator-assessed causality.

c: Death that occurred any time throughout the study.

Source: ISS Tables 4.2, 4.3.2, 4.3.3, 4.4, 5.7.1, 5.7.2, 6.1.1, 6.2, 7.1.1, 7.2.1 and 8.3; SCS Table 37, p 88

7.6 Clinical Laboratory Evaluations

Due to the nature of AML, all patients had abnormalities in one or more hematologic laboratory analytes at baseline. Myelosuppression is a consequence of AML, but may also occur as a result of drug treatment. During treatment, decreases in hemoglobin, neutrophils, and platelets were common abnormalities in both treatment arms. Mean nadir values were similar in patients receiving Dacogen or cytarabine for ANC, hemoglobin, lymphocytes, and

platelet count, and white blood cell counts were slightly lower in the Dacogen arm compared with cytarabine-treated patients. There was no indication of cumulative toxicity with respect to myelosuppressive effects during continued Dacogen treatment at least through Cycle 15 (1 year of treatment). There appears to be no discernable effect of Dacogen on nonhematologic clinical laboratory values. In Study 016, there did not appear to be any clinically relevant differences between Dacogen and cytarabine in the incidence of reported nonhematologic laboratory abnormalities, taking into account the longer duration of Dacogen treatment. Although glucose-related abnormalities were reported frequently as AEs, a review of the laboratory results suggests that treatment with Dacogen does not have an effect on glucose metabolism.

7.7 Vital Signs and Physical Exam

Overall, physical examination findings in the pooled Dacogen group are consistent with those expected for an aging oncology patient population. There were no clinically relevant trends in mean changes from baseline over time for any vital sign parameter except decreases in weight in the Dacogen arm, and to a lesser extent, the cytarabine group early during treatment.

7.8 Electrocardiograms

Routine electrocardiograms were only required at baseline in Study 016. The percentage of patients with clinically significant electrocardiogram abnormalities at baseline was similar between the Dacogen and TC arms. Transient, mild tachycardia was reported as an AE in 5.0% and 5.9% of patients in the Dacogen and TC arms, respectively. Atrial fibrillation was also frequently reported as an AE, and occurred in a similar percentage of patients across treatment arms (6.7% and 8.4% for Dacogen and TC arms, respectively). There were no reports of QT prolongation.

7.9 Safety in Special Populations and Situations

There did not appear to be any clinically relevant differences in the overall safety profile of Dacogen when analyzed by sex, age, race, or impaired renal function. As might be expected, however, patients with more severe disease—as indicated by unfavorable cytogenetic risk, ECOG PS 2, or myeloblast count > 30%—did have a slightly worse safety profile.

7.9.1 Age, Race, and Sex

In Study 016, there was no increase in the incidence of nonfatal SAEs with increasing age; Table 35 provides an overview of safety as a function of age for Dacogen and cytarabine in Study 016. A higher percentage of males than females in the Dacogen arm of Study 016 had reported SAEs of neutropenia (8.1% vs 3.9%) and pyrexia (11.9% vs 6.8%). This trend was not observed for cytarabine.

Table 35 Overview of Adverse Event Profile, by Age (Safety Population)

	Dacogen N = 238			Cytarabine N = 208		
Patients with AEs, n (%)	**< 65 yr (n = 3)**	**65 - 74 yr (n = 143)**	**≥ 75 yr (n = 92)**	**< 65 yr (n = 1)**	**65 -7 4 yr (n = 126)**	**≥ 75 yr (n = 81)**
Any AE	3 (100)	142 (99.3)	92 (100)	1 (100)	126 (100)	81 (100)
Grade 3 or 4 AEs	3 (100)	130 (90.9)	87 (94.6)	1 (100)	110 (87.3)	75 (92.6)
Serious AEs	2 (66.7)	112 (78.3)	80 (87.0)	1 (100)	88 (69.8)	62 (76.5)
Discontinuation due to AE	1 (33.3)	60 (42.0)	37 (40.2)	0	58 (46.0)	39 (48.1)
AEs leading to dose delay	1 (33.3)	44 (30.8)	28 (30.4)	1 (100)	36 (28.6)	21 (25.9)
AEs leading to dose reduction	0	22 (15.4)	10 (10.9)	0	14 (11.1)	6 (7.4)
AEs with outcome of death[a]	0	38 (26.6)	32 (34.8)	0	34 (27.0)	21 (25.9)

All events are treatment emergent.
Abbreviations: AE = adverse event.
a: As reported on AE page of case report form (CRF).
Source: ISS Tables 4.1.3.1, 4.1.3.2, 4.1.3.3; SCS Table 49, p 118

7.9.2 Impaired Renal Function

There are no data on the use of Dacogen in patients with renal dysfunction; therefore, Dacogen should be used with caution in these patients. Adverse events related to renal toxicity are discussed in Section 7.5.4 and Table 32.

7.9.3 Unfavorable Cytogenetic Risk

As might be anticipated, patients with unfavorable cytogenetic risk at baseline generally had a less favorable safety profile than patients with intermediate cytogenetic risk. However, the proportion of patients with at least one AE leading to death was slightly higher among patients with intermediate cytogenetic risk, primarily due to a higher rate of fatal infection. Among all Dacogen-treated patients, nonfatal SAEs were reported in a similar percentage of patients with intermediate-risk and unfavorable-risk cytogenetics. Overall, the incidence of commonly reported nonfatal SAEs was comparable between the two subgroups.

7.9.4 ECOG Performance Status

The proportion of patients receiving Dacogen who had a baseline ECOG PS of 2 in the two studies (Study 016 and Study 017) was relatively small (23.2%). No trend of increased incidence of AEs was observed with worsening baseline ECOG PS in Study 016. The proportion of patients who died was similar between the ECOG subgroups (88.9% for patients with ECOG PS 0-1 and 89.7% for patients with ECOG PS 2). Progressive disease was more frequently reported as the cause of death among patients with ECOG PS 0-1 (49.8%) than ECOG PS 2 (35.3%), whereas AEs were more frequently reported as the cause of death among patients with ECOG PS 2 (47.1%) compared with ECOG PS 0-1 (28.9%). The overall incidence of nonfatal SAEs was similar in Dacogen-treated patients with an ECOG PS 0-1

(75.6%) and PS 2 (79.4%), and there were no particular nonfatal SAEs that occurred in a higher percentage of patients in either subgroup.

7.9.5 Drug-Drug Interactions

No formal drug interaction studies with Dacogen have been conducted. In vitro studies in human liver microsomes suggest that Dacogen is unlikely to inhibit or induce cytochrome P450 enzymes. In vitro metabolism studies have suggested that Dacogen is not a substrate for human liver cytochrome P450 enzymes. As plasma protein binding of Dacogen is negligible (< 1%), interactions due to displacement of more highly protein-bound drugs from plasma proteins are not expected.

In Study 016, all patients received concomitant medications. Based on a review of SAE data, discontinuations, and deaths, there did not appear to be any interactions between Dacogen and the concomitant treatments administered in that trial.

7.10 Safety Profile of Dacogen in Study 017

The overall safety profile of Dacogen in Study 017 is shown in Table 36.

Table 36 Safety Profile of Dacogen, Study 017

Adverse Event Parameter	Patients, n (%) (N = 55)
Any grade TEAE	55 (100)
Grade 3 - 4 TEAEs	45 (81.8)
Grade 3 - 5 TEAEs	47 (85.5)
Serious TEAEs[a]	40 (72.7)
TEAEs requiring dose intervention	
Discontinuation of treatment due to TEAE	10 (18.2)
TEAE(s) leading to dose delay	23 (41.8)
TEAE(s) leading to dose reduction	1 (1.8)
AEs with an outcome of death	17 (30.9)

Abbreviations: TEAE = treatment-emergent adverse event.
a: Incidence of serious TEAEs included death.
Source: SCS Table 9; ISS Tables 4.1.1, 4.3.1.1, and 6.4.

In Study 017, the most common TEAEs were fatigue, nausea, and pyrexia. The incidence of febrile neutropenia and pneumonia were lower than in Study 016. All TEAEs regardless of causality that were reported by at least 10% of patients are shown in Table 37.

Table 37 Common Adverse Events Reported in ≥ 10% of Patients, Study 017

Preferred Term[a]	Dacogen (N = 55)
Patients with ≥ 1 AE, n (%)	**55 (100)**
Fatigue	37 (67.3)
Nausea	28 (50.9)
Pyrexia	24 (43.6)
Constipation	23 (41.8)
Diarrhea	22 (40.0)
Dyspnea	22 (40.0)
Edema peripheral	20 (36.4)
Febrile neutropenia	17 (30.9)
Asthenia	17 (30.9)
Hypokalemia	16 (29.1)
Cough	16 (29.1)
Vomiting	16 (29.1)
Dizziness	15 (27.3)
Anemia	14 (25.5)
Neutropenia	14 (25.5)
Headache	13 (23.6)
Thrombocytopenia	12 (21.8)
Hypocalcemia	10 (18.2)
Insomnia	10 (18.2)
Pneumonia	9 (16.4)
Disease progression	9 (16.4)
Hypoalbuminemia	9 (16.4)
Anorexia	9 (16.4)
Pain in extremity	8 (14.5)
Abdominal pain	8 (14.5)
Leukopenia	7 (12.7)
Urinary tract infection	7 (12.7)
Hyponatremia	6 (10.9)

Abbreviation: AE = adverse event.
a: Table includes AEs of any grade (Grade 1 to 5). A patient with multiple occurrences of an AE is counted only once at the maximum grade at which the event occurred; only treatment-emergent events are included.
Source: SCS Table 10; Appendix Table 6 and ISS Table 4.2

7.11 Post-Marketing Experience

Post-marketing reports of AEs received since Dacogen became commercially available in May 2006 have been reviewed and processed on an ongoing basis according to regulatory requirements. Post-marketing safety data are consistent with the known safety profile for Dacogen as reflected in the current US package insert.[1]

7.12 Overall Safety Conclusions

Dacogen was well tolerated by patients with AML in studies Study 016 and Study 017.

- The safety profile was consistent with the known safety profile of Dacogen in patients with MDS,[1] and there were no new safety signals observed in Study 016. It is noteworthy that the post-marketing safety profile of Dacogen has remained essentially unchanged and consistent with the approved label since it became commercially available in 2006.
- Treatment duration was approximately 2-fold longer in the Dacogen arm (4 versus 2 cycles), suggesting that Dacogen was well tolerated, and the safety profiles of Dacogen and cytarabine were similar.
- As expected, the most prevalent AEs were related to myelosuppression (cytopenias and febrile neutropenia). There was a numerically higher incidence of myelosuppression in the Dacogen arm, but this is unlikely to be clinically significant in the context of AML.
- AEs were generally manageable with standard medical care given by oncologists.
- The rate of discontinuation due to a TEAE was comparable between treatment arms.
- The incidence of 30-day all-cause mortality was low (8%) and similar in both treatment arms.
- There were no clinically meaningful differences in the incidence of infection, bleeding, cardiac AEs, or major central nervous system AEs between treatment arms.

8.0 BENEFIT/RISK SUMMARY

8.1 Unmet Medical Need in AML

Treatment options for elderly AML patients are limited because these patients are either not candidates for or choose not to receive standard induction chemotherapy because of poor tolerability and treatment outcomes. Furthermore, there are no approved therapies for AML patients who do not receive standard induction chemotherapy. Thus, there is an unmet medical need for new agents with established clinical benefit and a favorable safety profile in this patient population.

8.2 Clinical Benefit

The clinical benefit of Dacogen compared with TC (cytarabine or SC) was demonstrated in a large, well-controlled, randomized, Phase 3 trial (Study 016), one of the largest prospective trials ever conducted in an elderly AML population. The primary analysis of OS at the original cutoff date of 28 October 2009, demonstrated a median OS of 7.7 months in the Dacogen arm versus 5.0 months in the TC arm. Although not statistically significant, this analysis demonstrated a clinically meaningful trend for an OS advantage in the Dacogen arm, which when viewed in the context of other efficacy findings, represents a clinical benefit to these patients. The updated analysis of OS, with 1 additional year of follow up, demonstrated the same 2.7-month improvement in the median OS with a nominal *p* value of 0.037 in favor of the Dacogen arm. This analysis supports the conclusion that the OS difference observed in the primary analysis represents a real treatment effect. The median OS of 7.6 months in supportive Study 017 was also consistent with the Study 016 result.

In addition, sensitivity analyses of OS that censored for subsequent DMT were conducted using both the original and the more updated datasets. These analyses adjusted for the imbalance in subsequent DMT and demonstrated a statistically significant OS advantage in favor of Dacogen, thus providing further support for the treatment effect of Dacogen in this patient population.

Assessment of pre-specified subgroups also showed a consistent OS advantage in favor of Dacogen across nearly all subgroups. One notable exception was the small subgroup of patients in Western Europe in which the hazard ratio for OS appeared to favor the TC arm. To address this, additional exploratory analyses were performed. Kaplan-Meier analysis of OS by region revealed that patients randomized to Dacogen had similar survival outcomes across regions. In the TC arm, patients treated in Asia, Eastern Europe, and North America/Australia all had similar survival outcomes, whereas patients in Western Europe (n = 34) had unusually favorable survival outcomes compared with the other geographic regions. A much higher proportion of patients in Western Europe randomized to the TC arm (35%) received subsequent treatment with a hypomethylating agent (mostly 5-azacytidine) compared with only 8% in the Dacogen arm. In the other geographic regions, use of post-study hypomethylating agents was infrequent. This could have contributed to the anomalous OS in the TC arm in Western Europe.

Results from secondary and tertiary endpoints provide further evidence of clinical benefit. In Study 016 the rate of CR + CRp for the two arms was 17.8% vs 7.8% favoring Dacogen

treatment with an odds ratio of 2.5 (95% CI: 1.40, 4.78; $p = 0.001$). In supportive Study 017, the morphologic CR rate was similar (23.6%). The median duration of response for the 43 Dacogen responders in Study 016 was 8.3 months. The median time to relapse for the 13 responders in Study 017 was 18.2 months. Achieving durable CRs is an accepted indicator of clinical benefit in patients with acute leukemias.[14] Achieving a CRp has also been shown to confer longer survival and has been validated as a measure of clinically meaningful response when used in conjunction with CR rates.[33] Analyses of EFS and PFS further corroborate the efficacy of Dacogen for treatment of AML. In Study 016, median EFS and PFS were both significantly longer for patients in the Dacogen arm, and consistent outcomes were observed in Study 017.

Taken together, these data provide evidence of a clinically meaningful treatment effect and support the clinical benefit of Dacogen in this setting.

8.3 Clinical Risk

Dacogen was first granted marketing authorization in 2006, and its safety profile has been well established over years of use treating patients with MDS in the United States and 30 other countries throughout the world. The data presented in this sNDA demonstrate a similar safety profile in elderly patients with AML. There were no new safety findings.

In Study 016, the median duration of treatment with Dacogen (4.4 months) was approximately 2-fold longer than in the TC arm (2.4 months), indicating that Dacogen was well tolerated. Importantly, the rate of discontinuation due to a TEAE was comparable between treatment arms in Study 016, and the rate of early deaths (i.e., 30-day all-cause mortality) was low (8.8% in the Dacogen arm and 8.0% in the TC arm) and similar across treatment groups. These rates of early deaths compare favorably with those reported in the literature for induction chemotherapy in similar patient populations (17% to 54%).[34,35] The most frequently reported causes of death were similar to those generally reported in patients with AML, and included disease progression, infections (e.g., pneumonia, sepsis/septic shock) and bleeding events. Fatal infections were reported in approximately 10% of patients in both treatment arms. Deaths attributed to a TEAE of the CNS were primarily due to a hemorrhagic event, which was associated with thrombocytopenia in most cases, and in most cases those patients had low platelet counts at baseline. A careful review of these deaths did not reveal any pattern that would signal a safety issue with Dacogen. No other remarkable differences in mortality were observed in the overall or subgroup analyses.

Myelosuppression and AEs related to myelosuppression (e.g., thrombocytopenia, anemia, neutropenia, and febrile neutropenia) are common causes of morbidity and mortality in both treated and untreated patients with AML. As expected, myelosuppression was a common toxicity in the AML trials. Multilineage cytopenias are a hallmark of AML. Indeed, baseline laboratory values show that the majority of patients had cytopenias at study entry and that Grade 3 and 4 myelosuppression was numerically more common in the Dacogen arm compared with the TC arm, but the differences were not clinically significant in the context of AML. The increased incidence of Grade 3 or 4 myelosuppression in the Dacogen arm may also reflect the longer treatment period in the Dacogen arm. Assessment of ANC by cycle demonstrated that approximately 60% of patients had laboratory values consistent with Grade 3 or 4 neutropenia at baseline, and there was a somewhat higher numerical incidence of neutropenia in the Dacogen arm compared with the TC arm, but these differences are unlikely

to be clinically meaningful in the context of this disease. Importantly, there was no dramatic change from baseline in either group. In general, myelosuppression is manageable with standard medical care given by oncologists. Low platelet counts can be managed by platelet transfusions, while anemia can be treated with erythroid growth factors and RBC transfusions.

Infections and bleeding events were frequently reported in both treatment groups. Infections tended to occur early in treatment and did not increase in frequency over time. These results suggest that patients enrolled in Study 016 were predisposed to infection because of their underlying disease. Importantly, there did not appear to be any clinically relevant differences in the incidence of infections or bleeding events between Dacogen- and cytarabine-treated patients. Furthermore, these toxicities can be successfully managed in the outpatient setting by delaying treatment cycles to allow adequate hematologic recovery, and with the use of blood products, hematopoietic growth factors such as granulocyte-colony stimulating factor and granulocyte-macrophage colony stimulating factor, and anti-infective agents.

In summary, Dacogen was generally well tolerated, with a low rate of early deaths, especially compared with induction chemotherapy. Elderly patients over the age of 75 years tolerated Dacogen as well as younger patients. The safety findings observed in Study 016 were entirely consistent with the known safety profile of Dacogen in the MDS population and also comparable to that of low-dose cytarabine, one of the few treatment options available to elderly AML patients who do not receive induction chemotherapy. No cumulative toxicity or new safety signals were observed with Dacogen in this setting. The established and manageable safety profile of Dacogen supports its use in elderly patients with AML.

8.4 Benefit-Risk Conclusions

The totality of the efficacy and safety data indicate that Dacogen (20 mg/m^2 once daily for 5 consecutive days every 4 weeks) has a favorable benefit-risk profile in AML patients $\geq$ 65 years of age who do not receive standard induction chemotherapy.

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10.0 APPENDIX

Appendix A

Table 38 Patients With Fatal (Grade 5) Cardiac-Related Adverse Events, Study 016 and Study 017 (Safety Population)

Study No. Treatment Group Patient ID	Age (y) Sex (M/F)	Significant Medical History	Baseline ECOG PS	Cause of Death	Study Day of AE Onset	Days From Last Dose to Death
Study 016 Dacogen						
1067-003	81/F	Atrial fibrillation, hypertension	1	Supraventricular tachycardia	895	13
3044-142	77/M	Myocardial ischemia, MI, arteriosclerosis	2	Cardiac arrest	182	24
3044-206	75/M	Atrial fibrillation, hypertension, diabetes, cardiovascular insufficiency, MI, COPD	2	Cardiac disorder	18	18
3045-077	77/M	Diabetes	2	Cardiac arrest	166	15
3048-172	69/M	Hypertension, tachyarrhythmia	1	Cardiac failure	70	18
3055-110	73/M	COPD, lobar pneumonia	1	Cardiac failure	15	14
3070-128	72/F	Diabetes, hypertension	2	Cardiac arrest	42	23
3070-135	75/F	Coagulopathy, hypertension	1	Cardiac failure	113	25
3070-297	76/F	Diabetes, hypertension	1	Left ventricular failure	39	9
3070-345	79/M	Cardiac failure chronic, myocardial ischemia, MI, hypertension	2	Cardiac arrest	102	17
3070-352	65/M	Hypertension, cardiovascular insufficiency	1	Cardiac failure congestive	54	22
3070-466	76/M	COPD, hypokalemia, dehydration	2	Cardiac arrest	19	15
3079-125	68/M	Myocardial ischemia, MI, angina pectoris	2	Acute MI	8	4
				Pulmonary edema	8	
Cytarabine						

1164-195	74/M	Atrial fibrillation, hypertension, diabetes, cardiac failure congestive, COPD	1	Atrial fibrillation	131	30
3044-152	85/M	Myocardial ischemia, arteriosclerosis, atrial fibrillation, cardiovascular insufficiency	2	Cardiorespiratory arrest	12	2
3070-250	65/F	Hypertension	1	Cardiac arrest	116	26
3070-397	73/M	Hypertension, cardiac failure chronic	1	Cardiac arrest	33	24
3071-270	67/F	CAD, hypertension, infection, hepatitis, hemorrhage	1	Cardiac failure, acute	11	3
7005-332	72/M	Atrial fibrillation	0	Cardiac arrest	151	25
Study 017						
Dacogen						
1048-012	63/M	High blood pressure, MI, cardiomegaly, CHF	1	Myocardial infarction	38	9

Abbreviations: AE = adverse event; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ECOG PS = Eastern Cooperative Oncology Group performance status; MI = myocardial infarction.
Source: SCS Table 36, p 85-86

Table 39 Patients With Fatal (Grade 5) CNS-Related Adverse Events, Study 016 and Study 017 (Safety Population)

Study No.[a] Treatment Group Patient ID	Age (y) Sex (M/F)	Significant Medical History	Baseline ECOG PS	Cause of Death	Study Day of AE Onset	Days From Last Dose to Death
Study 016 Dacogen						
3039-415	75/F	Hemorrhage subcutaneous Concomitant meds including etamsylate and aminocaproic acid (hemorrhage prophylaxis)	2	Subarachnoid hemorrhage	18	12
3048-066[a]	70/M	Anemia, thrombocytopenia, arrhythmia supraventricular	1	Cerebral hemorrhage	11	4
3070-287	74/M	Concomitant meds including etamsylate (thrombocytopenia)	1	Hemorrhage intracranial	41	8
3070-378	68/M	Thrombocytopenia	1	Hemorrhage intracranial	625	9
3071-036	70/M	Thrombocytopenia, angina pectoris Concomitant meds including enalapril and allopurinol (arterial hypertension)	1	Cerebral infarction	81	21
3073-235	78/F	DVT, arterial ischemia	2	Hemorrhage intracranial	75	19
5001-251	66/M	Type 2 diabetes, hypertension	1	Cerebral hemorrhage	15	15
Cytarabine						
3048-409	73/M	Type 2 diabetes, MDS, anemia, sinus tachycardia	1	Coma Rectal hemorrhage Hemorrhagic diathesis	110 105 107	10
3060-322	71/M	Hypertension	1	Hemorrhage intracranial	672	12

Abbreviations: AE = adverse event; CNS = central nervous system; DVT = deep venous thrombosis; ECOG PS = Eastern Cooperative Oncology Group performance status; MDS = myelodysplastic syndrome.
a: No fatal CNS-related events occurred in Study 017.
Source: SCS Table 39, p 90