

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIostatISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number: 21-790/N-000
Drug Name: Dacogen[®] (decitabine) for Injection
Indication: Myelodysplastic Syndromes (MDS)
Applicant: SuperGen
Date: 10/29/2004
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Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

The data and analyses from the current submission showed that the Fisher's exact test for Overall Response Rate was significant in favor of Dacogen compared to Supportive Care, although the log-rank test for the Time to AML or Death was not significant. According to the protocol, the primary analyses support that Dacogen was more effective than Supportive Care for patients with Myelodysplastic Syndromes (MDS) with respect to the Overall Response Rate.

1.2 Brief Overview of Clinical Studies

Study D-007 was an open-label, parallel-group, randomized trial conducted in USA and Canada. Adult patients enrolled were with MDS meeting FAB classification and IPSS High-risk, Intermediate-1, and Intermediate-2 prognostic scores. Response was measured following every second dosing cycle (12 weeks) in Dacogen treatment arm and every 12 weeks in patients randomized to Supportive Care arm. One-hundred and seventy (170) patients were randomized (89 in Dacogen; 81 in Supportive Care). Co-primary endpoints were the Overall Response Rate (CR + PR) and the Time to AML or Death. The primary analyses were Fisher's exact test for the Overall Response Rate (CR + PR), and the log-rank test for the Time to AML or Death.

1.3 Statistical Issues and Findings

Study D-007 shows that the Overall Response Rate (CR + PR) in Dacogen was 17% (15/89) vs. 0% in Supportive Care ($p=0.001$). The median Time to the AML or Death was 340 days in Dacogen arm and 219 days in Supportive Care arm ($p = 0.160$).

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2. Introduction

2.1 Overview

Decitabine (5-aza-2'-deoxycytidine; NSC 127716) was first synthesized in Czechoslovakia in 1964. Anti-leukemic activity was first demonstrated in mice in 1968 and confirmed in mice by a second group in 1978. Anti-leukemia activity was demonstrated in children with chemotherapy-resistant acute leukemia in 1981. Further interest was stimulated in this compound when it was demonstrated to be more potent than cytosine arabinoside and to induce cell differentiation. This offered a potential two-pronged attack in hematological malignancies: cytotoxicity at high doses and cell differentiation to a non-neoplastic cell line at lower doses. The applicant assumed responsibility for IND 33,929 and the clinical development program for Dacogen on October 8, 1999 from Pharmachemie. Based on the results of two Phase II clinical trials (PCH 95-11 and PCH 97-19) of low-dose Dacogen in Myelodysplastic Syndromes (MDS) and several publications, the applicant prepared a Phase III protocol. This protocol was discussed with the Agency at an End of Phase II meeting on January 31, 2001. Dacogen was granted Orphan Drug Status for use in patients with MDS in the US on November 22, 2000 and in the EU on February 14, 2003.

In this review, only Study D-007 will be discussed. Study D-007 was an open-label, parallel-group, randomized trial conducted in USA and Canada. Patients aged 18 or older enrolled were with MDS meeting FAB classification and IPSS High-risk, Intermediate-1, and Intermediate-2 prognostic scores. Response was measured following every second dosing cycle (12 weeks) in Dacogen treatment arm and every 12 weeks in patients randomized to Supportive Care arm. One-hundred and seventy patients were randomized (89 in Dacogen; 81 in Supportive Care). Co-primary endpoints were the Overall Response Rate (CR + PR) and the Time to AML or Death. The primary analyses were Fisher's exact test for the Overall Response Rate (CR + PR), and the log-rank test for the Time to AML or Death.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

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3. Statistical Evaluation

3.1 Evaluation of Efficacy

Text, tables and figures presented in Section 3.1.1 to 3.1.7 are mainly from the applicant's Study

Report.

3.1.1 Objective of Study D-007

The objective of this multi-center clinical study was to demonstrate the superiority of Dacogen Injection over standard medical care (i.e. Supportive Care) for treatment of adults (18 years or older) with Myelodysplastic Syndromes (MDS).

3.1.2 Study Design

This was an open-label, parallel-group, randomized trial of 170 adult patients with histologically confirmed MDS by FAB classification (including CMML with WBC < 12,000/ μ L) and IPSS \geq 0.5; age \geq 18 years; ECOG or WHO performance status zero-two; renal and hepatic function (creatinine \leq 2 mg/dL, bilirubin \leq 1.5 mg/dL, SGPT \leq 2 times ULN).

Scheduled Procedures and Activities. Patients were screened against entry criteria during a prestudy visit. During the pre-study and baseline visits a medical history was taken, physical examination performed, BM aspirates, biopsies and cytogenetics were obtained, blood samples were drawn for CBC, serum chemistries, and serum hCG, and the EORTC Quality of Life questionnaire was completed. Eligible patients were assigned to Dacogen or Supportive Care treatment arms in a 1:1 ratio, and were stratified by study center, IPSS classification and type of MDS (i.e., *de novo* vs. secondary). Both treatment arms received standard medical care/supportive care for MDS (i.e., general guidance on the use of PRBCs and/or platelets; prophylactic fluoroquinolone antibiotics; colony-stimulating factors; erythropoietin and thrombopoietin; and hospitalization). In addition, patients in Dacogen arm received Dacogen Injection as nine, three-hour infusions over three days per cycle. Every six weeks the clinical investigator performed a medical history, physical examination, serum chemistries and the EORTC Quality of Life questionnaire. Every 12 weeks, a BM aspirate and biopsy were performed to evaluate response to treatment. At the end of study, the final BM aspirate/biopsy, CBC, serum chemistries/hCG and EORTC Quality of Life questionnaire were performed. A single interim analysis was performed after 45 patients had reached the event of "AML or Death."

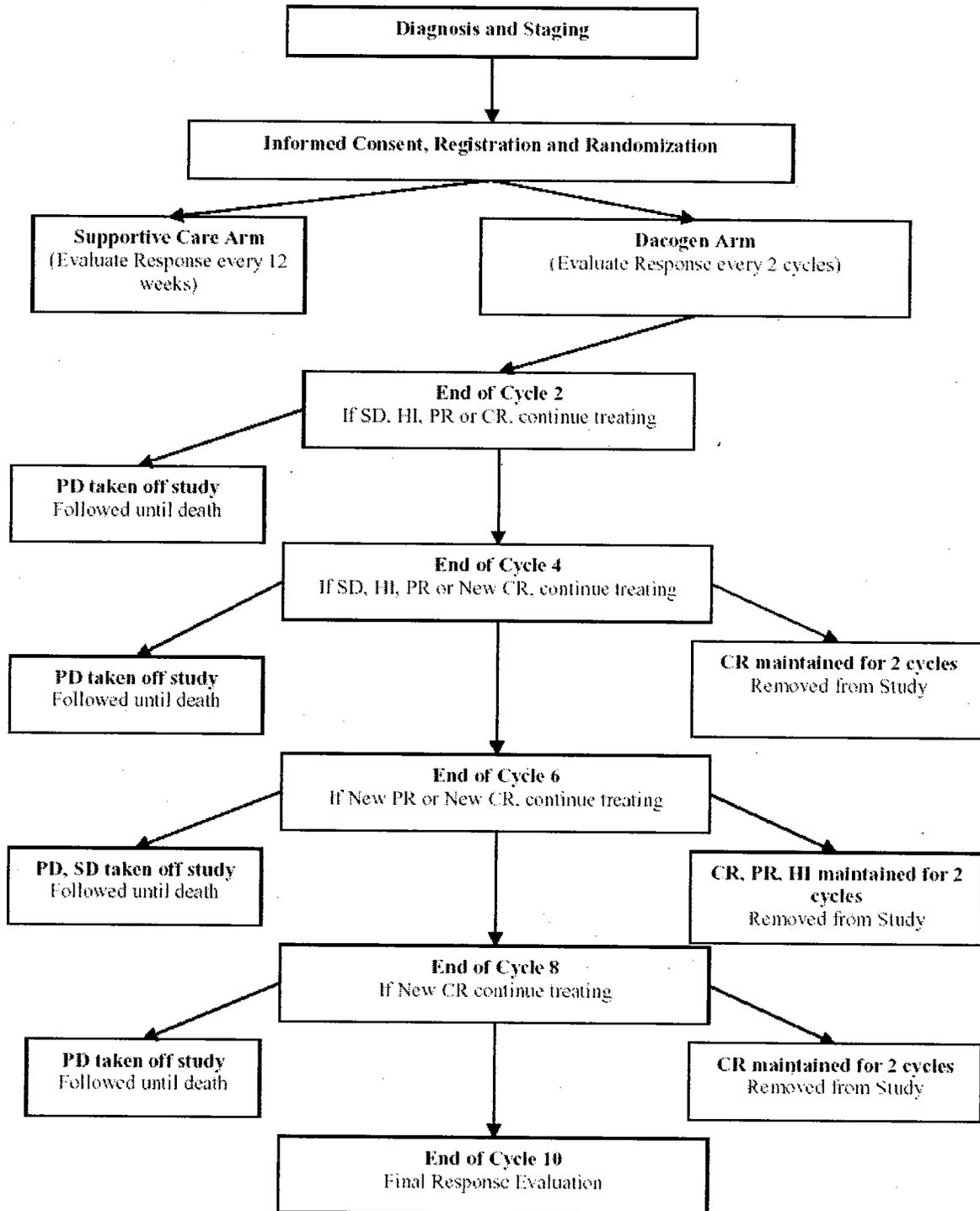
Treatment Schema. Figure 3.1.2.1 illustrates the flow of treatment decisions made for individual patients during the conduct of the clinical trial. Response was evaluated in patients randomized to Supportive Care arm once every 12 weeks, which was approximately equal to the timing of two treatment cycles in Dacogen arm. Patients in Supportive Care arm received standard medical treatment for MDS and could be followed for up to 60 weeks. Patients receiving Supportive Care who progressed to AML (\leq 30% bone marrow blasts) or experienced rapidly progressive disease (RPD), as defined by MDS International Working Group (IWG) criteria, were initially allowed to crossover and receive Dacogen therapy. This practice was stopped by Protocol Amendment 2 after three patients had crossed over and received Dacogen. Amendment 2 allowed any patient who had converted to AML and thus had reached their endpoint, to participate in a separate Phase II Dacogen

companion study SGI-DAC-011, an open-label Phase II trial of low-dose Dacogen in patients with acute myeloid leukemia (AML) following myelodysplastic syndrome.

Patients randomized to Dacogen arm received a 15 mg/m^2 dose of Dacogen Injection in a three-hour i.v. infusion that was given every eight hours for three days. This constituted one treatment cycle and was repeated approximately every six weeks, depending on recovery from myelosuppression. Response was evaluated in patients randomized to Dacogen arm once every two treatment cycles, or approximately once every 12 weeks. Treatment decisions for patients receiving Dacogen were made at the end of each two treatment cycles. Dacogen patients received up to ten treatment cycles depending on their response. After any two cycles, Dacogen patients were taken off study if they demonstrated progressive disease (PD), as defined by MDS IWG. Other patients were continued on treatment as specified in Figure 3.1.2.1 for a maximum of ten cycles. As medically necessary, patients in both treatment arms were given supportive care, which consisted of packed red blood cell (PRBC) and/or platelets; prophylactic fluoroquinolone antibiotics; colony-stimulating factors; erythropoietin and thrombopoietin; and hospitalization.

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Figure 3.1.2.1 Study Treatment Schema for Clinical Protocol



3.1.3 Efficacy Measures

The co-primary efficacy endpoints are 1) the Overall Response Rate (CR + PR) based on patients' best responses to randomized treatment; and 2) the Time to AML or Death. These were defined as follows:

- Achievement of complete (CR) was measured in serial BM aspirates showing < 5% myeloblasts without dysplastic changes. The peripheral blood evaluation must have met the following absolute values for at least the last two months: Hb > 11 g/dL (without transfusions or use of erythropoietin); neutrophils $\geq 1500/\mu\text{L}$ (without use of myeloid growth factor); platelets $\geq 100,000/\mu\text{L}$ (without use of a thrombopoetic agent); and no blasts or dysplasia.
- Achievement of partial response (PR) used the same absolute criteria as CR, except a successful outcome in BM criteria required the blasts to be decreased $\geq 50\%$ over pre-treatment values or for the patient to have a less advanced MDS FAB classification versus pretreatment.
- For CR, PR (and hematological improvement (HI)), the IWG criteria had a provision for patients receiving cyclic myelosuppressive therapy. The provision states that "in some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 2-month period. Such patients can be included in the response category into which they fit at the time the therapy is started".
- Date of AML conversion was based on the first date with a diagnosis of AML ($\geq 30\%$ BM blasts per FAB criteria) assessed by BM aspirates or biopsies; but, AML conversion could be based on peripheral blast counts alone (CBC), if no marrow was available (specific agreement between sponsor and the Agency on February 6, 2004).
- Death was self-evident and authenticated by a death certificate, corroborated by a family member or determined through inquiry in the social security database.

Secondary endpoints included the evaluation of survival, transfusion requirements, rate of febrile neutropenia, percentage of patients achieving Improvement (CR + PR + HI), Quality of Life, and cytogenetic responses.

3.1.4 Statistical Analysis Plan

The primary analysis for the Overall Response Rate (CR + PR) was Fisher's exact test.

The primary analysis for the Time to AML or Death was the log-rank test. The generalized Wilcoxon test result was also presented.

The overall Type-1 error rate was maintained at a maximum of 5% by applying a Bonferroni correction. A single interim analysis was planned following 45 events with the final analysis conducted on the first 92 events. Statistical significance was determined using a one-sided O'Brien-Fleming boundary of $\alpha = 0.0026$ and $\alpha = 0.024$ at the interim and final analyses, respectively. A maximum p-value of 0.024 was required to establish statistical significance using a two-sided analysis for either co-primary endpoint. Statistical significance ($p \leq 0.024$) of either co-primary endpoint was considered

by the applicant to confirm that the response observed with Dacogen was superior to that of Supportive Care.

Sample size was based on the primary efficacy variable of the Time to AML or Death, which was 80 per treatment arm to allow for 80% power in analyzing 92 events using a two-sided test at a significance level of 0.05 and to detect a ten month difference (22 vs. 12 months). This sample size was based on a projected six-month patient accrual period and a total study period of 24 months. A single interim analysis was planned after 45 events.

3.1.5 Protocol Amendments

The study protocol was issued by the applicant on November 14, 2000 and filed to IND No. 33,929. The first patient was enrolled in the study on July 24, 2001. The protocol was amended four times on the following dates: February 26, 2001 (Amendment 1), June 4, 2001 (Amendment 2), October 26, 2001 (Amendment 3), and April 24, 2002 (Amendment 4). The first two amendments were implemented prior to the enrollment of the first patient in the study. Less than 10 patients were enrolled prior to Amendment 3 and 53 patients were enrolled at the time Amendment 4 was implemented. Amendment 3, which was implemented to increase study enrollment and gather controlled experience with Dacogen in Intermediate-1 patients, may have negatively impacted the composite endpoint of the Time to AML or Death. None of the other amendments are considered to have impacted study outcome.

Amendment 1: the Overall Response Rate (CR + PR) was rejected as the applicant's primary efficacy endpoint by the Agency at the EOP2 meeting held January 31, 2001. This amendment was written to replace the applicant's primary endpoint with that recommended by the Agency, the Time to AML or Death.

Changes: Based on the new primary endpoint, the sample size was recalculated. Other changes to the protocol included all those recommended by the Agency from review of the Phase 3 clinical protocol and those additional ones emerging from the Agency EOP2 meeting including: modifications to secondary endpoints (clarifying Improvement Rate [CR + PR + HI] as defined by MDS IWG criteria); clarification of FAB classifications used in the inclusion criteria (i.e., that AML was $\geq 30\%$ blasts vs. the previous definition of $\geq 20\%$ blasts used by WHO); addition of randomization strata (i.e., prior MDS treatment and type of MDS); clarifications of allowed treatments given as supportive care; and clarification of the Quality of Life performance scales.

Amendment 2: This amendment was written to maintain the integrity of the study's randomization by eliminating crossover of patients from Dacogen arm to Supportive Care arm. A second objective was to provide for a sample size adjustment that would permit an interim analysis at 45 events.

Changes: The amendment eliminated the crossover provision for patients with rapidly progressive disease (RPD) who were receiving Supportive Care and provided those patients converting to AML

an option to enroll in a separate protocol, SGI-DAC-011 (An open-label Phase II trial of low-dose decitabine in patients with acute myeloid leukemia (AML) following myelodysplastic syndromes). In addition, the sample size increase to 80 patients per group was clarified as needed to accommodate an interim analysis. The use of prescribed drugs was clarified as being a protocol violation if taken within seven days of starting study drug (30 days for investigational product).

Amendment 3: This amendment was implemented to increase study enrollment and gather experience with Dacogen in Intermediate-1 patients.

Changes: This amendment expanded the inclusion criteria to allow enrollment of intermediate-1 patients (IPSS) into the trial and allowed patients to receive Dacogen injections at a clinic or at home.

Amendment 4: This amendment was written to clarify that patients had to reach the AML event prior to allowing them to leave the study for SGI-DAC-011 study, reduce the number of randomization strata (to simplify the procedure), enforce and clarify inclusion/exclusion criteria.

Changes: This amendment revised the minimum percent blasts to $\geq 30\%$ for Supportive Care patients moving to protocol DAC-SGI-011 (i.e. no waivers allowed for 20–30% blasts). It also required that BMs for cytogenetics be acquired in all patients prior to study entry, modified the definition of hematologic recovery prior to study entry (fully recovered and off of all chemotherapy for four weeks and nitrosoureas and BM transplantation for six weeks), clarified which version of CTC was to be used, decreased the number of randomization strata to three (study center, IPSS classification and previous chemotherapy for MDS), indicated that Dacogen treatment was to start within seven-ten days of randomization and clarified that a retrospective review of all bone marrow slides and biopsies would be done by an independent expert for study eligibility and therapeutic response.

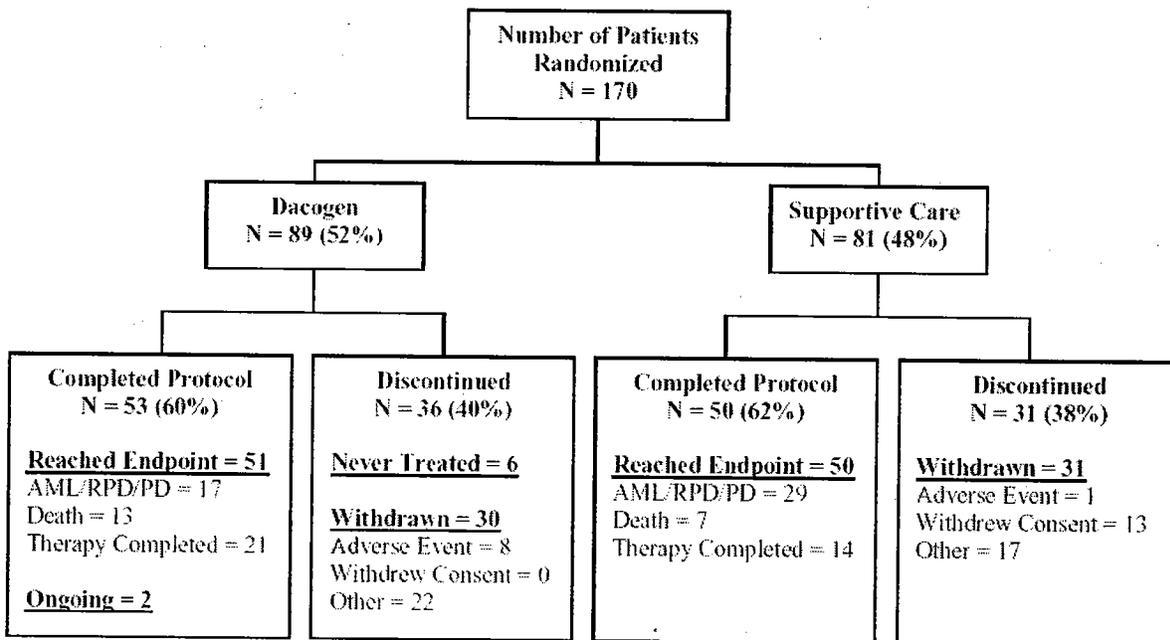
Changes in the Planned Analyses: All analyses of the primary endpoints were performed first, followed by the secondary endpoints and finally any exploratory analyses. According to Protocol Amendment 4, the randomization strata were simplified to include only study center, IPSS classification and Prior Treatment of MDS (chemotherapy vs. treatment-naïve). However, a mistake was made in implementing the amendment and Type of MDS was used in all remaining patients. All analyses that adjust for stratification will use Type of MDS instead of Prior Treatment of MDS as stipulated in the protocol. A revised statistical analysis plan was submitted to the Agency on March 12, 2004, in which coprimary endpoints of the Overall Response Rate (CR + PR) and the Time to AML or Death were to be used in the primary analyses. Fisher's exact test was to be used to analyze the Overall Response Rate (CR + PR).

3.1.6 Study Population

This clinical study report was based on 170 patients who were randomized from July 24, 2001 to January 12, 2004. Patients were enrolled at 23 of the 25 investigational centers. All patients were diagnosed by the investigator as having MDS by bone marrow aspirates and peripheral blood counts and categorized histologically according to the FAB criteria and IPSS classification. Figure 3.1.6.1 shows that the number of patients randomized was 89 to Dacogen and 81 to Supportive Care.

Six patients randomized to Dacogen never received study drug. These patients were shown as “never treated.” Three patients in the Supportive Care arm experienced disease progression, or crossed over to receive Dacogen (Patient 0143-500 was rapidly progressing disease (RPD) at end of Supportive Care and death at End-of-Study; Patient 1006-5042 was rapidly progressive disease (RPD) at end of Supportive Care and completed treatment per protocol at End-of-Study; Patient 1007-5039 was AML at the end of Supportive Care and death at End-of-Study).

Figure 3.1.6.1 Patient Disposition between Treatment Arms



The disposition of all patients as they discontinued study participation is provided in Table 3.1.6.1.

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Table 3.1.6.1 Reasons for Patient Discontinuation from Study

Reason for Discontinuation	Randomized to Dacogen N = 89 N (%)	Randomized to Supportive Care N = 81 N (%)
Completed Protocol	53 (60)	50 (62)
Therapy Completed	21 (24)	14 (17)
Progression of Disease (AML, RPD and PD)	17 (19)	29 (36)†
Death	13 (15)	7 (9)
Ongoing at Database Lock	2 (2)*	0 (0)
Discontinuations	36 (40)	31 (38)
Adverse Event	8 (9)	1 (1)
Patient Withdrew Consent	0 (0)	13 (16)
Never Treated	6 (7)‡	0 (0)
Other (total)	22 (25)	17 (21)
Delayed Cell Count Rebound	14 (16)	0 (0)
Patient ended therapy	2 (2)	3 (4)
Patient sought other treatment	2 (2)	3 (4)
Home administration failure	2 (2)	0 (0)
Patient non-compliance	1 (1)	3 (4)
Investigator discretion	1 (1)	3 (4)
Bone marrow or stem cell transplant	0 (0)	3 (4)
Non-related secondary cancer recurrence	0 (0)	2 (2)

*Two Dacogen patients (0143-5163 and 1025-5145) reported here as completed had finished six cycles of treatment and were still in follow-up at database lock without an "off study" form completed.

†Three patients in the Supportive Care arm experienced disease progression (Patient 0143-5007—RPD, Patient 1006-5042—RPD, Patient 1007-5039—AML) and are shown here in that group. Subsequently they were crossed over to receive Dacogen; the reasons for discontinuation at the end of Dacogen treatment were Death, Completed Treatment per Protocol and Death, respectively.

‡Six patients in the Dacogen arm were randomized to study drug, but never received it. These patients are shown as "never treated." These were patients 1003-5114/withdrew consent, 1008-5137/disease progression, 1033-5142/death, 1046-5115/patient ended therapy, 1046-5136/disease progression, and 1046-5144/disease progression.

Based on the primary reasons given for patients' discontinuations, patients in Dacogen arm were more likely to complete the study per protocol and less likely to withdraw informed consent;

however, adverse events and death were also more frequently cited reasons in Dacogen arm for discontinuing treatment. More patients in Supportive Care arm discontinued for progression of disease and/or withdrawal of consent.

Patients in Dacogen and Supportive Care treatment arms had similar demographics, disease characteristics and Baseline performance (Table 3.1.6.2). Most patients were elderly (over 65 years of age), white males with de novo MDS that had been diagnosed a median of approximately 30 weeks prior to start of study.

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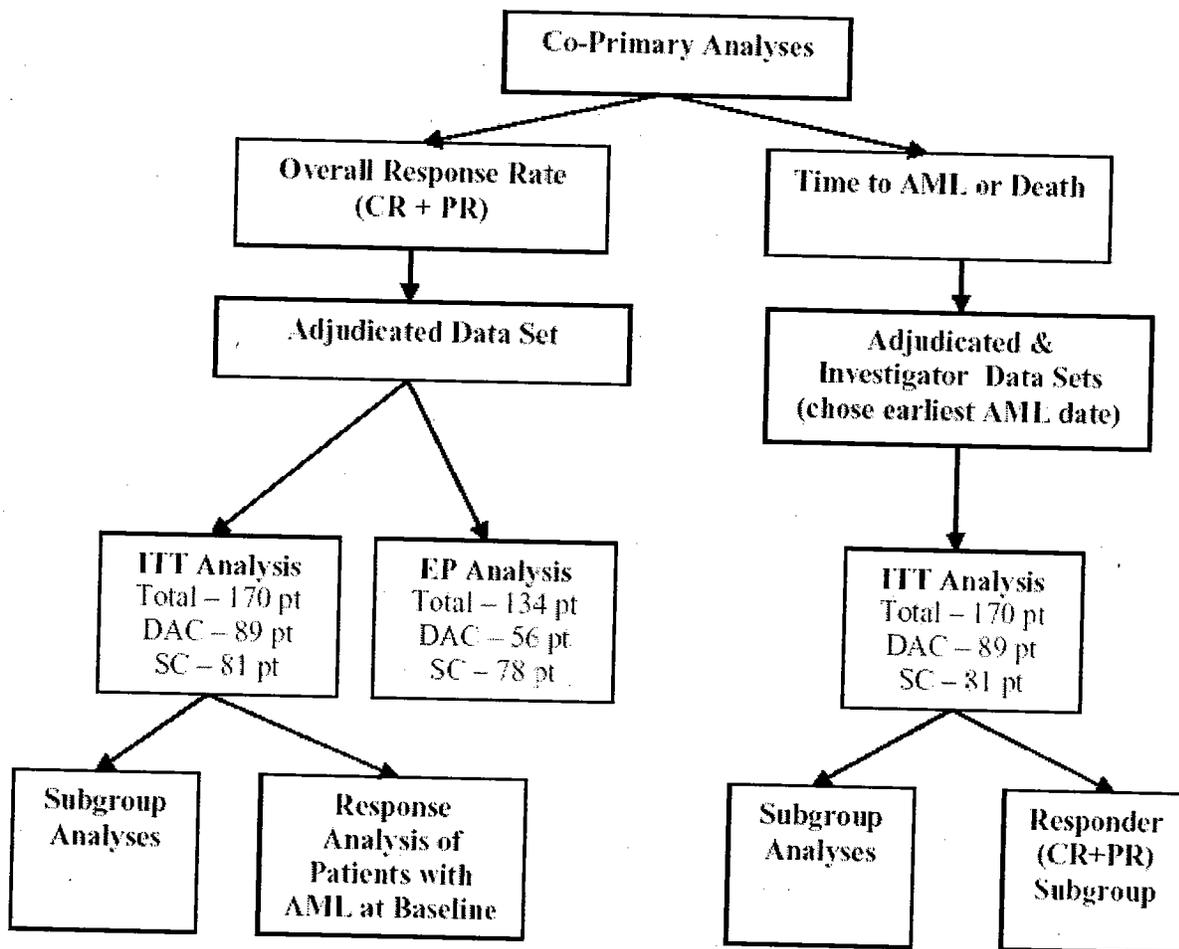
Table 3.1.6.2 Baseline Demographics and Other Patient Characteristics

Demographic or Other Patient Characteristic	Dacogen N = 89	Supportive Care N = 81	p-value ¹
Age (years) Mean (\pm SD) Median (IQR) (Range: min-max)	69 (\pm 10) 70 (65-76) (31-85)	67 (\pm 10) 70 (62-74) (30-82)	0.113
Age Stratification < 65 years (n (%)) 65-74 years (n (%)) \geq 75 years (n (%))	23 (26) 42 (47) 24 (27)	30 (37) 35 (43) 16 (20)	0.254
Gender Male (n (%)) Female (n (%))	59 (66) 30 (34)	57 (70) 24 (30)	0.662
Ethnic Origin White (n (%)) Black (n (%)) Other (n (%))	83 (93) 4 (4) 2 (2)	76 (94) 2 (2) 3 (4)	0.717
Weeks Since MDS Diagnosis Mean (\pm SD) Median (IQR) (Range: min-max)	86 (\pm 131) 29 (10-87) (2-667)	77 (\pm 119) 35 (7-98) (2-865)	0.914
Percent Blasts in BM Mean (\pm SD) Median (IQR) (Range: min-max) Missing Values (%)	11 (\pm 8) 10 (4-17) — —	11 (\pm 8) 9 (5-16) — —	0.874
Type of MDS <i>De novo</i> (n (%)) Secondary (n (%))	77 (87) 12 (13)	70 (86) 11 (14)	1.000
Previous MDS Therapy Yes (n (%)) No (n (%))	27 (30) 62 (70)	19 (23) 62 (77)	0.388
IPSS Classification Intermediate-1 (n (%)) Intermediate-2 (n (%)) High Risk (n (%))	28 (31) 38 (43) 23 (26)	24 (30) 36 (44) 21 (26)	0.980
FAB Classification RA (n (%)) RARS (n (%)) RAEB (n (%)) RAEB-t (n (%)) CMML (n (%))	12 (13) 7 (8) 47 (53) 17 (19) 6 (7)	12 (15) 4 (5) 43 (53) 14 (17) 8 (10)	0.887

Intention-To-Treat (ITT) Analyses included all 170 (89 Dacogen and 81 Supportive Care) randomized patients (including the six patients randomized to Dacogen arm who never received study drug) for both the Overall Response Rate and the Time to AML or Death.

Efficacy data from the two crossover patients with RPD (exposed to Dacogen prior to reaching AML endpoint) are taken only from their participation in Supportive Care arm prior to crossover treatment with Dacogen. Figure 3.1.7.1 presents patient disposition in primary analyses.

Figure 3.1.7.1 Patient Disposition in Primary Analyses



For Evaluable Patient (EP) analyses: After excluding the six patients randomized to Dacogen arm who never received study drug and additional 12 patients (9 Dacogen and 3 Supportive Care) who were diagnosed as having AML at Baseline by Dr. Bennett’s expert interpretation of the BM, there are 74 Dacogen and 78 Supportive Care in EP for the Time to AML or Death analysis. Since response was evaluated in patients randomized to Dacogen arm once every two treatment cycles or

approximately once every 12 weeks, 18 patients in Dacogen who did not complete Cycle 2 were excluded in EP analysis for the Overall Response Rate. This approach eliminated 18 Dacogen patients because the criteria focused on removing Dacogen patients who had less than an adequate number of treatment cycles to provide a response. Consequently, there are 56 Dacogen and 78 Supportive Care in EP analysis for the Overall Response Rate

Overall Response Rate (CR+PR): In ITT analysis, Overall Response Rate in Dacogen patients was superior to that seen in Supportive Care arm ($p < 0.001$). There were no responders on Supportive Care arm. Seventeen percent (15/89) of patients randomized to Dacogen arm had either a complete or partial response. There were more CRs than PRs: eight CRs and seven PRs. Responses were durable with a median duration of 266 days (131–346). Median time to response was 89 days (55–153) as shown in Table 3.1.7.1. The median cycle to respond was Cycle 3.

Table 3.1.7.1 ITT and EP Analysis of Overall Adjudicated Response Rate (CR + PR)

Parameter	Dacogen	Supportive Care	p-values†
Intention to Treat Analysis	N = 89	N = 81	
Complete Response (CR)	8 (9%)	0 (0%)	–
Partial Response (PR)	7 (8%)	0 (0%)	–
Overall Response Rate (CR + PR)	15 (17%)	0 (0%)	< 0.001[‡]
Median time to (CR + PR) response (days) (Range)	89 (55-153)	(0)	–
Median Duration of (CR + PR) response (days)	266 (131-346)	(0)	–
Evaluable Patient Analysis	N = 56	N = 78	
Complete Response (CR)	6 (11%)	0 (0%)	–
Partial Response (PR)	6 (11%)	0 (0%)	–
Overall Response Rate (CR + PR)	12 (21%)	0 (0%)	< 0.001[‡]
Median time to (CR + PR) response (days) (Range)	89 (55-146)	(0)	–
Median Duration of (CR + PR) response (days)	277 (131-342)	(0)	–

[†]From two-sided Fisher's Exact Test for equal Overall Response (CR+PR) Rate.

[‡]In the co-primary endpoint model, a p-value of ≤ 0.024 was required to achieve statistical significance.

Time to AML or Death : The other co-primary efficacy endpoint was the Time to AML or Death. The date of progression to AML was taken from either the Adjudicated (Expert Reviewer) or Investigator Data Set, whichever provided the earliest diagnosis of AML.

The Time to the AML or Death analysis for ITT did not reach statistical significance (Table 3.1.7.2) although patients in Dacogen arm had a median Time to AML or Death of 121 days greater than that of patients in Supportive Care arm.

Table 3.1.7.2 Time to AML or Death* (ITT) at 92 Events

Parameter	Dacogen N = 89	Supportive Care N = 81	p-value [†]
Number of events (%)	46 (52)	46 (57)	0.043 ¹ , 0.160 ²
Median (95% CI) days	340 (285-407)	219 (148-379)	
Range days (min-max) [‡]	24-624	7-432	

[†] In the co-primary endpoint model, a p-value of ≤ 0.024 was required to achieve statistical significance.

* Reflects analysis after 92 events. Patients crossing over or never receiving randomized treatment are censored

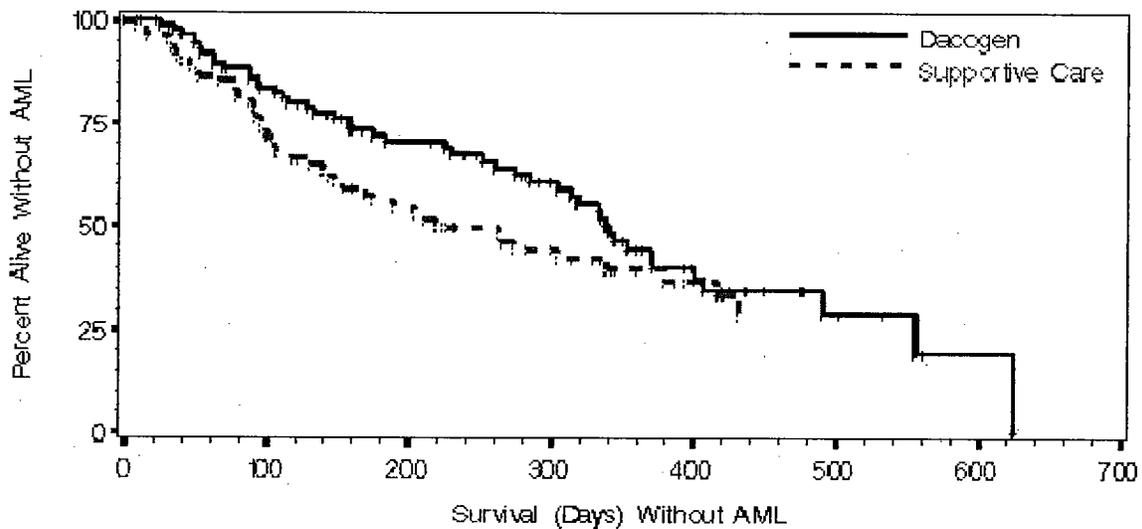
[‡] From actual events only

¹ From two-sided Wilcoxon test for homogeneity of survival distributions

² From two-sided log-rank test for homogeneity of survival distributions

From Kaplan-Meier curves in Figure 3.1.7.2, Dacogen treatment arm showed early separation. This separation of the Kaplan-Meier curves suggests that progression to AML or death was longer in Dacogen arm.

Figure 3.1.7.2 Time to AML or Death* (ITT) at 92 Events



For the Time to AML or Death, the log-rank test gives p-value of .756 for EP analysis.

Table 3.1.7.3 Time to AML or Death (EP)

Population	Parameter	Dacogen	Supportive Care	p-value
EP	Total	74	78	.756
	Number of events (%)	47 (64%)	45 (58%)	
	Median days	334 (260-371)	263 (154-417)	
	Range days	24-624	7-493	

3.1.8 Reviewer's Analysis

For the analysis of the Time to AML or Death, this reviewer believes that the log-rank test which gave p-value .160 was the original planned primary analysis although the applicant presented results of both the log-rank test and Wilcoxon test in the submission. The applicant stated in Amendment 4 "The treatment groups will be compared by the log-rank test. The generalized Wilcoxon test results also will be presented."

The reviewer validated the applicant's efficacy analyses.

The Overall Response Rate Analysis: Fisher's exact test gives p-values .001 for both ITT and EP analyses for the Overall Response Rate.

Table 3.1.8.1 Analysis of Overall Adjudicated Response Rate (CR + PR)

Population	Parameter	Dacogen	Supportive Care	p-value
ITT	Total	89	81	.001
	Response Rate (%)	15 (17%)	0 (0%)	
EP	Total	56	78	.001
	Response Rate (%)	12 (21%)	0 (0%)	

There was only center (number 1033) in Canada which had 4 subjects in Decogen and 1 in Supportive Care. Analysis by country will not be performed. Table 3.1.8.2 presents the number of responses by center for ITT.

Table 3.1.8.2 Overall Response Rate by Center (responses/total) (ITT)

Center	Dacogen N=89	Supportive Care N=81
0062	0/1	
0087		0/2
0120	0/4	0/5
0121	3/5	0/1
0143	1/5	0/5
0160		0/2
1000		0/1
1001	0/1	0/3
1002	2/7	0/2
1003	2/11	0/9
1004	1/4	0/5
1005	0/2	0/2
1006	1/15	0/19
1007	1/1	0/3
1008	2/7	0/3
1011	0/1	
1025	0/3	0/4
1030	0/3	0/3
1032	1/2	0/2
1033	1/4	0/1
1034		0/2
1036	0/1	
1046	0/12	0/7

Center 0121 had the highest unbalance response rate. Fisher’s exact test gives p-value .0003 after removing center 0121.

Transfusion Status: This analysis is one secondary analysis of the applicant.

Responder vs. Non-Responder: As defined by the MDS IWG criteria used to rate best hematologic response, patients achieving a CR or PR must be transfusion independent for a minimum of eight weeks in the absence of growth factors during the period of response.

Independent vs. Dependent: Patients were considered transfusion independent at Baseline if they had no transfusions during the eight-week period prior to randomization or transfusion dependent at Baseline if they received any RBC or platelet transfusion during that time. Patients were considered transfusion independent on study if they had no transfusions during at least one six-week period (i.e., weeks 1–6, 7–12, etc.). Patients were considered transfusion dependent on study if they had one or more transfusions and were not transfusion-free for at least one six-week period.

Evaluation of Transfusion Status in Patients Who Responded: Prior to study, (9/15) of responders were transfusion dependent with all nine patients being RBC transfusion dependent and four patients were also platelet transfusion dependent. All 15 responders met MDS IWG criteria and became transfusion independent during the time of response. Table 3.1.8.3 presents transfusion status for Decogen responders.

Table 3.1.8.3 Transfusion Status for Decogen Responders

RBC	
Dependent at Baseline	N=9
Dependent to Independent	9 (100%)
Independent at Baseline	N=6
Remained Independent	6 (100%)
PLATELETS	
Dependent at Baseline	N=4
Dependent to Independent	4 (100%)
Independent at Baseline	N=11
Remained Independent	11 (100%)

The Time to AML or Death Analysis: For the Time to AML or Death, the log-rank test gives p-value .160 for ITT, and .756 for EP analyses. For EP analysis, the applicant redefined first 92 events after excluding patients who had major protocol violations. The advantage of redefining first 92 events is to have planned 80% power for the analysis. Notice that number of events in Decogen arm for EP is greater than that in ITT due to redefining first 92 events.

Table 3.1.8.4 Time to AML or Death at 92 Events

Population	Parameter	Dacogen	Supportive Care	p-value
ITT	Total	89	81	.160
	Number of events (%)	46 (52%)	46 (57%)	
	Median (95% CI) days	340 (285-407)	219 (148-379)	
	Range days (min-max)	24-624	7-432	
EP	Total	74	78	.756
	Number of events (%)	47 (64%)	45 (58%)	
	Median days	334 (260-371)	263 (154-417)	
	Range days	24-624	7-493	

If one defines first 92 events for ITT and then excludes patients who had major protocol violations, the log-rank test gives p-value .385. The number of total events 84 is less than 92 because there are no redefined events after excluding patients who had major protocol violations.

Table 3.1.8.5 Time to AML or Death without Redefining 92 Events

Population	Parameter	Dacogen	Supportive Care	p-value
EP	Total	74	78	.385
	Number of events (%)	41 (55%)	43 (55%)	
	Median (95% CI) days	335 (260-400)	265 (154-417)	
	Range days	24-624	7-432	

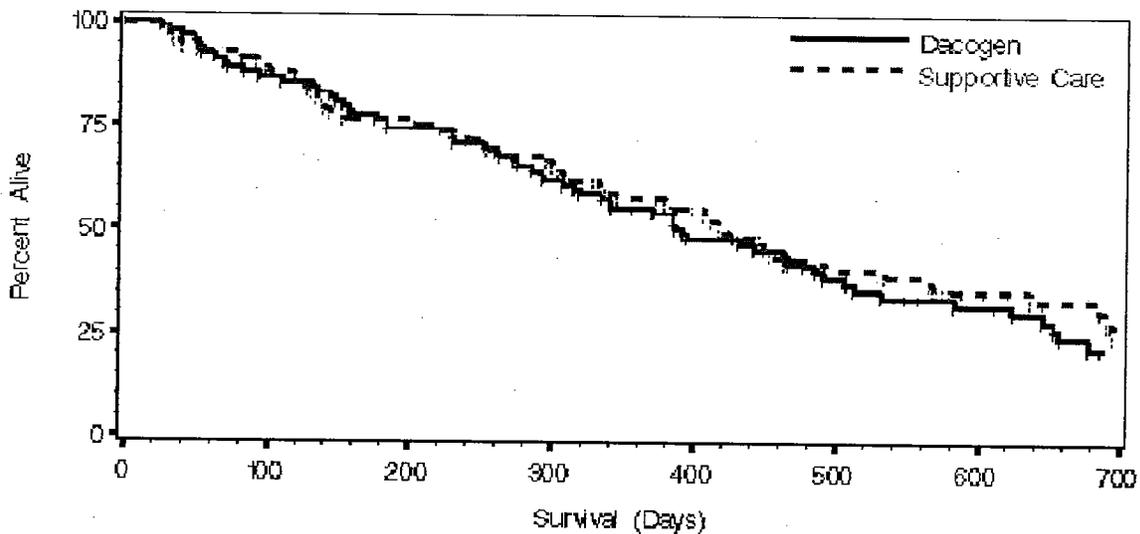
For a sensitivity analysis, Table 3.1.8.6 presents survival analysis, which is a secondary analysis of the applicant. The number of events reflects follow-up cut-off date of August 10, 2004, where patients crossing over or never receiving randomized treatment are censored. The log-rank test gives p-value .636. The median survival for the two arms were: 391 days for Dacogen compared to 417 days for Supportive Care.

Table 3.1.8.6 Survival Analysis for All Events (ITT)

Population	Parameter	Dacogen	Supportive Care	p-value
ITT	Total	89	81	.636
	Number of events (%)	64 (72%)	55 (68%)	
	Median (95% CI) days	391 (314-491)	417 (333-534)	
	Range days	24-745	30-797	

Figure 3.1.8.1 presents Kaplan-Meier curves for all events.

Figure 3.1.8.1 Kaplan-Meier Curve for All Events (ITT)



An interim data analysis based on the 45 first events for the Time to AML or Death was included in a briefing document for the meeting on April 25, 2003, between the applicant and the Agency after study enrollment was completed. The revised statistical analysis plan was submitted to the Agency on March 12, 2004 to add the Overall Response Rate as co-primary endpoint when the interim analysis was already performed. The trial continued after the interim analysis because p-value from the log-rank test for 45 events was not significant.

3.2 Evaluation of Safety

See Clinical Review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Table 4.1.1 and 4.1.2 present co-primary endpoints by gender, race, and age, respectively. Median Days are from K- M estimates.

Table 4.1.1 Time to AML or Death by Subgroup (ITT)

Subgroup	Characteristics		Dacogen	Supportive Care
Gender	Male	Number of Events Median Days	29/59 (49%) 335	28/57 (49%) 339
	Female	Number of Events Median Days	17/30 (57%) 344	18/24 (75%) 138
Race	White	Number of Events Median Days	43/83 (52%) 338	44/76 (58%) 219
	Non-white	Number of Events Median Days	3/6 (50%) 344	2/5 (40%)
Age	< 65	Number of Events Median Days	11/23 (48%) 370	15/30 (50%) 265
	65-74	Number of Events Median Days	20/42 (48%) 334	19/35 (54%) 304
	≥ 75	Number of Events Median Days	15/24 (63%) 335	12/16 (75%) 143

Table 4.1.2 Response Rate by Subgroup (ITT)

Subgroup	Characteristics	Dacogen	Supportive Care
Gender	Male	7/59 (12%)	0/57 (0%)
	Female	8/30 (27%)	0/24 (0%)
Race	White	13/83 (16%)	0/76 (0%)
	Non-white	2/6 (33%)	0/5 (0%)
Age	< 65	6/23 (26%)	0/30 (0%)
	65-74	7/42 (17%)	0/35 (0%)
	≥ 75	2/24 (8%)	0/16 (0%)

4.2 Other Special/Subgroup Populations

There is no analysis performed for other populations.

5. Summary and Conclusions**5.1 Statistical Issues and Collective Evidence**

Study D-007 shows that the Overall Response Rate (CR + PR) in Dacogen was 17% (15/89) vs. 0% in Supportive Care (p=0.001). The median Time to AML or Death was 340 days in the Dacogen arm and 219 days in the Supportive Care arm (p = 0.160).

5.2 Conclusions and Recommendations

The data and analyses from the current submission showed that the Fisher's exact test for the Overall Response Rate was significant in favor of Dacogen compared to Supportive Care, although the log-rank test for the Time to AML or Death was not significant. According to the protocol, the primary analyses support that Dacogen was more effective than Supportive Care for patients with Myelodysplastic Syndromes (MDS) with respect to the Overall Response Rate.

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