CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

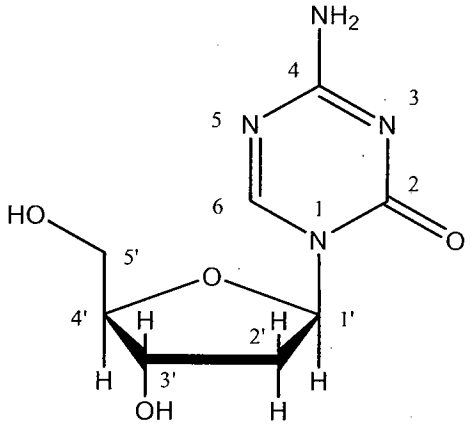
21-790

APPROVED LABELING

DACOGEN™ (DECITABINE) FOR INJECTION

DESCRIPTION

Dacogen™ (decitabine) for Injection contains decitabine (5-aza-2'-deoxycytydine), an analogue of the natural nucleoside 2'-deoxycytidine. Decitabine 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. Its chemical name is 4-amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one and it has the following structural formula:



Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; sparingly soluble in water and soluble in dimethylsulfoxide (DMSO).

Dacogen™ (decitabine) for Injection is a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 mL, single dose, glass vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation *in vitro,* which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-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 decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine.

Pharmacokinetics

No information is available on the pharmacokinetics of decitabine at the indicated dosage of 15 mg/m^2. Patients with advanced solid tumors received a 72-hour infusion of decitabine at 20 to 30 mg/m^2/day.

Decitabine pharmacokinetics were characterized by a biphasic disposition. The total body clearance (mean ± SD) was 124 ± 19 L/hr/m^2, and the terminal phase elimination half-life was 0.51 ± 0.31 hr. Plasma protein binding of decitabine is negligible (<1%).

The exact route of elimination and metabolic fate of decitabine is not known in humans. One of the pathways of elimination of decitabine appears to be deamination by cytidine deaminase found principally in the liver but also in granulocytes, intestinal epithelium and whole blood.

Special Populations

The effects of renal or hepatic impairment, gender, age or race on the pharmacokinetics of decitabine have not been studied.

Drug-Drug Interactions

Drug interaction studies with decitabine have not been conducted. In vitro studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. *In vitro* metabolism studies have suggested that decitabine is not a substrate for the human liver cytochrome P450 enzymes. As plasma protein binding of decitabine is negligible (<1%), interactions due to displacement of more highly protein bound drugs from plasma proteins are not expected.

CLINICAL STUDIES

Phase 3 Trial

A randomized open-label, multicenter, controlled trial evaluated 170 adult patients with myelodysplastic syndromes (MDS) meeting French-American-British (FAB) classification criteria and International Prognostic Scoring System (IPSS) High-Risk, Intermediate-2 and Intermediate-1 prognostic scores. Eighty-nine patients were randomized to Dacogen therapy plus supportive care (only 83 received Dacogen), and 81 to Supportive Care (SC) alone. Patients with Acute Myeloid Leukemia (AML) were not intended to be included. Of the 170 patients included in the study, independent review (adjudicated diagnosis) found that 12 patients (9 in the Dacogen arm and 3 in the SC arm) had the diagnosis of AML at baseline. Baseline demographics and other patient characteristics in the Intent-to-Treat (ITT) population were similar between the 2 groups, as shown in **Table 1**.

Table 1 Baseline Demographics and Other Patient Characteristics (ITT)

Demographic or Other Patient Characteristic	Dacogen N=89	Supportive Care N=81
Age (years)		
Mean (±SD)	69±10	67±10
Median (IQR)	70 (65-76)	70 (62-74)
(Range: min-max)	(31-85)	(30-82)
Gender n (%)		
Male	59 (66)	57 (70)
Female	30 (34)	24 (30)
Race n (%)		
White	83 (93)	76 (94)
Black	4 (4)	2 (2)
Other	2 (2)	3 (4)
Weeks Since MDS Diagnosis		
Mean (±SD)	86±131	77±119
Median (IQR)	29 (10-87)	35 (7-98)
(Range: min-max)	(2-667)	(2-865)
Previous MDS Therapy n (%)		
Yes	27 (30)	19 (23)
No	62 (70)	62 (77)
RBC Transfusion Status n (%)		
Independent	23 (26)	27 (33)
Dependent	66 (74)	54 (67)
Platelet Transfusion Status n (%)		
Independent	69 (78)	62 (77)
Dependent	20 (22)	19 (23)
IPSS Classification n (%)		
Intermediate–1	28 (31)	24 (30)
Intermediate–2	38 (43)	36 (44)
High Risk	23 (26)	21 (26)

Table 1 Baseline Demographics and Other Patient Characteristics (Cont'd)

Demographic or Other Patient Characteristic	Dacogen N=89	Supportive Care N=81
FAB Classification n (%)		
RA	12 (13)	12 (15)
RARS	7 (8)	4 (5)
RAEB	47 (53)	43 (53)
RAEB-t	17 (19)	14 (17)
CMML	6 (7)	8 (10)

Patients randomized to the Dacogen arm received Dacogen intravenously infused at a dose of 15 mg/m^2 over a 3-hour period, every 8 hours, for 3 consecutive days. This cycle was repeated every 6 weeks, depending on the patient's clinical response and toxicity. Supportive care consisted of blood and blood product transfusions, prophylactic antibiotics, and hematopoietic growth factors. Co-primary endpoints of the study were overall response rate (complete response + partial response) and time to AML or death. Responses were classified using the MDS International Working Group (IWG) criteria; patients were required to be RBC and platelet transfusion independent during the time of response. Response criteria are given in **Table 2**:

Table 2 Response Criteria for Phase 3 Trial*

Complete Response (CR) ≥ 8 weeks	**Bone Marrow**	**On repeat aspirates:** • < 5% myeloblasts • No dysplastic changes
	Peripheral Blood	**In all samples during response:** • Hgb > 11g/dL (no transfusions or erythropoietin) • ANC ≥ 1500/μL (no growth factor) • Platelets ≥ 100,000/μL (no thrombopoietic agent) • No blasts and no dysplasia
Partial Response (PR) ≥ 8 weeks	**Bone Marrow**	**On repeat aspirates:** • ≥ 50% decrease in blasts over pretreatment values OR • Improvement to a less advanced MDS FAB classification
	Peripheral Blood	**Same as for CR**

* Cheson BD, Bennett JM, et al. Report of an International Working Group to Standardize Response Criteria for MDS. *Blood.* 2000; 96:3671-3674.

The overall response rate (CR+PR) in the ITT population was 17% in Dacogen-treated patients and 0% in the SC group (p<0.001). (**See Table 3**) The overall response rate was 21% (12/56) in Dacogen-treated patients considered evaluable for response (i.e., those patients with pathologically confirmed MDS at baseline who received at least 2 cycles of treatment). The median duration of response (range) for patients who responded to Dacogen was 288 days (116-388) and median time to response (range) was 93 days (55-272). All but one of the Dacogen-treated patients who responded did so by the fourth cycle. Benefit was seen in an additional 13% of Dacogen-treated patients who had hematologic improvement, defined as a response less than PR lasting at least 8 weeks, compared to 7% of SC patients. Dacogen treatment did not significantly delay the median time to AML or death versus supportive care.

Table 3 Analysis of Response (ITT)

Parameter	Dacogen N=89	Supportive Care N=81
Overall Response Rate (CR+PR) †	**15 (17%)****	**0 (0%)**
Complete Response (CR)	8 (9%)	0 (0%)
Partial Response (PR)	7 (8%)	0 (0%)
Duration of Response		
Median time to (CR+PR) response Days (range)	93 (55-272)	NA
Median Duration of (CR+PR) response Days (range)	288 (116-388)	NA

**** p-value <0.001 from two-sided Fisher's Exact Test comparing Dacogen vs. Supportive Care.**

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

All patients with a CR or PR were RBC and platelet transfusion independent in the absence of growth factors.

Responses occurred in patients with an adjudicated baseline diagnosis of AML.

Phase 2 Studies

Two additional open-label, single-arm, multicenter studies in Europe were conducted to evaluate the safety and efficacy of Dacogen in MDS patients with any of the FAB subtypes. Dacogen was intravenously infused at a dose of 15 mg/m^2 over a 4-hour period, every 8 hours, on days 1, 2 and 3 of week 1 every 6 weeks (1 cycle). The results of the Phase 2 studies were consistent with the results of the Phase 3 trial with overall response rates of 26% (N=66) and 24% (N=98).

INDICATIONS AND USAGE

Dacogen is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all French-American-British 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.

CONTRAINDICATIONS

Dacogen is contraindicated in patients with a known hypersensitivity to decitabine.

WARNINGS

Pregnancy – Teratogenic effects: Pregnancy Category D

Dacogen may cause fetal harm when administered to a pregnant woman. The developmental toxicity of decitabine was examined in mice exposed to single IP (intraperitoneal) injections (0, 0.9 and 3.0 mg/m^2, approximately 2% and 7% of the recommended daily clinical dose, respectively) over gestation days 8, 9, 10 or 11. No maternal toxicity was observed but reduced fetal survival was observed after treatment at 3 mg/m^2 and decreased fetal weight was observed at both dose levels. The 3 mg/m^2 dose elicited characteristic fetal defects for each treatment day, including supernumerary ribs (both dose levels), fused vertebrae and ribs, cleft palate, vertebral defects, hind-limb defects and digital defects of fore- and hind-limbs. In rats given a single IP injection of 2.4, 3.6 or 6 mg/m^2 (approximately 5, 8 or 13% the daily recommended clinical dose, respectively) on gestation days 9-12, no maternal toxicity was observed. No live fetuses were seen at any dose when decitabine was injected on gestation day 9. A significant decrease in fetal survival and reduced fetal weight at doses greater than 3.6 mg/m^2 was seen when decitabine was given on gestation day 10. Increased incidences of vertebral and rib anomalies were seen at all dose levels, and induction of exophthalmia, exencephaly, and cleft palate were observed at 6.0 mg/m^2. Increased incidence of foredigit defects was seen in fetuses at doses greater than 3.6 mg/m^2. Reduced size and ossification of long bones of the fore-limb and hind-limb were noted at 6.0 mg/m^2.

There are no adequate and well-controlled studies in pregnant women using Dacogen. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Dacogen. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Use in Males

Men should be advised not to father a child while receiving treatment with Dacogen. and for 2 months afterwards. (See **PRECAUTIONS**: **Carcinogenesis, Mutagenesis, and Impairment of Fertility** for discussion of pre-mating effects of decitabine exposure on male fertility and embryonic viability.)

PRECAUTIONS

General

Treatment with Dacogen is associated with neutropenia and thrombocytopenia. Complete blood and platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be adjusted as described in **DOSAGE AND ADMINISTRATION**. Clinicians should consider the need for early institution of growth factors and/or antimicrobial agents for the prevention or treatment of infections in patients with MDS. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles, and may not necessarily indicate progression of underlying MDS.

There are no data on the use of Dacogen in patients with renal or hepatic dysfunction; therefore, Dacogen should be used with caution in these patients. While metabolism is extensive, the cytochrome P450 system does not appear to be involved. In clinical trials, Dacogen was not administered to patients with serum creatinine > 2.0 mg/dL, transaminase greater than 2 times normal, or serum bilirubin > 1.5 mg/dL.

Information for Patients

Patients should inform their physician about any underlying liver or kidney disease.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Dacogen.

Men should be advised not to father a child while receiving treatment with Dacogen, and for 2 months afterwards.

Laboratory Tests

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

Drug-Drug Interactions

No formal assessments of drug-drug interactions between decitabine and other agents have been conducted. (See **CLINICAL PHARMACOLOGY**.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No formal carcinogenicity evaluation of decitabine has been performed.

The mutagenic potential of decitabine was tested in several *in vitro* and *in vivo* systems. Decitabine increased mutation frequency in L5178Y mouse lymphoma cells, and mutations were produced in an *Escherichia coli lac-I* transgene in colonic DNA of decitabine-treated mice. Decitabine caused chromosomal rearrangements in larvae of fruit flies.

The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice administered a single 3 mg/m^2 IP injection (approximately 7% the recommended daily clinical dose) on day 10 of gestation. Body weights of males and females exposed *in utero* to decitabine were significantly reduced relative to controls at all postnatal time points. No consistent effect on fertility was seen when female mice exposed *in utero* were mated to untreated males. Untreated females mated to males exposed *in utero* showed decreased fertility at 3 and 5 months of age (36% and 0% pregnancy rate, respectively). In male mice given IP injections of 0.15, 0.3 or 0.45 mg/m^2 decitabine (approximately 0.3% to 1% the recommended clinical dose) 3 times a week for 7 weeks, decitabine did not affect survival, body weight gain or hematological measures (hemoglobin and WBC counts). Testes weights were reduced, abnormal histology was observed and significant decreases in sperm number were found at doses $\geq$ 0.3 mg/m^2. In females mated to males dosed with $\geq$ 0.3 mg/m^2 decitabine, pregnancy rate was reduced and preimplantation loss was significantly increased.

Pregnancy

Teratogenic Effects: Category D. See WARNINGS section

Nursing Mothers:

It is not known whether decitabine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from Dacogen in nursing infants, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

The safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Of the total number of patients exposed to Dacogen in the phase 3 study, 61 of 83 patients were age 65 and over, while 21 of 83 patients were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has

not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Most Commonly Occurring Adverse Reactions: neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia.

Adverse Reactions Most Frequently (≥ 1%) Resulting in Clinical Intervention in the Phase 3 Trial in the Dacogen Arm:

Discontinuation: thrombocytopenia, neutropenia, pneumonia, Mycobacterium avium complex infection, cardio-respiratory arrest, increased blood bilirubin, intracranial hemorrhage, abnormal liver function tests.

Dose Delayed: neutropenia, pulmonary edema, atrial fibrillation, central line infection, febrile neutropenia.

Dose Reduced: neutropenia, thrombocytopenia, anemia, lethargy, edema, tachycardia, depression, pharyngitis.

Discussion of Adverse Reactions Information

Dacogen was studied in 2 single-arm Phase 2 studies (N = 66, N = 98) and 1 controlled Phase 3 (Supportive Care) study (N = 83 exposed to Dacogen). The data described below reflect exposure to Dacogen in 83 patients in the Phase 3 MDS trial. In the Phase 3 trial, patients received 15 mg/m^2 intravenously every 8 hours for 3 days every 6 weeks. The median number of Dacogen cycles was 3 (range 0 to 9).

Table 4 presents all adverse events regardless of causality occurring in at least 5% of patients in the Dacogen group and at a rate greater than supportive care.

Table 4 Adverse Events Reported in ≥5% of Patients in the Dacogen Group and at a Rate Greater than Supportive Care in Phase 3 MDS Trial

	Dacogen N = 83 (%)	Supportive Care N = 81 (%)
Blood and lymphatic system disorders		
Neutropenia	75 (90)	58 (72)
Thrombocytopenia	74 (89)	64 (79)
Anemia NOS	68 (82)	60 (74)
Febrile neutropenia	24 (29)	5 (6)
Leukopenia NOS	23 (28)	11 (14)
Lymphadenopathy	10 (12)	6 (7)
Thrombocythemia	4 (5)	1 (1)
Cardiac disorders		
Pulmonary edema NOS	5 (6)	0 (0)
Eye disorders		
Vision blurred	5 (6)	0 (0)
Gastrointestinal disorders		
Nausea	35 (42)	13 (16)
Constipation	29 (35)	11 (14)
Diarrhea NOS	28 (34)	13 (16)
Vomiting NOS	21 (25)	7 (9)
Abdominal pain NOS	12 (14)	5 (6)
Oral mucosal petechiae	11 (13)	4 (5)
Stomatitis	10 (12)	5 (6)
Dyspepsia	10 (12)	1 (1)
Ascites	8 (10)	2 (2)
Gingival bleeding	7 (8)	5 (6)
Hemorrhoids	7 (8)	3 (4)
Loose stools	6 (7)	3 (4)
Tongue ulceration	6 (7)	2 (2)
Dysphagia	5 (6)	2 (2)
Oral soft tissue disorder NOS	5 (6)	1 (1)
Lip ulceration	4 (5)	3 (4)
Abdominal distension	4 (5)	1 (1)
Abdominal pain upper	4 (5)	1 (1)
Gastro-esophageal reflux disease	4 (5)	0 (0)
Glossodynia	4 (5)	0 (0)
General disorders and administrative site disorders		

	Dacogen N = 83 (%)	Supportive Care N = 81 (%)
Pyrexia	44 (53)	23 (28)
Edema peripheral	21 (25)	13 (16)
Rigors	18 (22)	14 (17)
Edema NOS	15 (18)	5 (6)
Pain NOS	11 (13)	5 (6)
Lethargy	10 (12)	3 (4)
Tenderness NOS	9 (11)	0 (0)
Fall	7 (8)	3 (4)
Chest discomfort	6 (7)	3 (4)
Intermittent pyrexia	5 (6)	3 (4)
Malaise	4 (5)	1 (1)
Crepitations NOS	4 (5)	1 (1)
Catheter site erythema	4 (5)	1 (1)
Catheter site pain	4 (5)	0 (0)
Injection site swelling	4 (5)	0 (0)
Hepatobiliary Disorders		
Hyperbilirubinemia	12 (14)	4 (5)
Infections and Infestations		
Pneumonia NOS	18 (22)	11 (14)
Cellulitis	10 (12)	6 (7)
Candidal infection NOS	8 (10)	1 (1)
Catheter related infection	7 (8)	0 (0)
Urinary tract infection NOS	6 (7)	1 (1)
Staphylococcal infection	6 (7)	0 (0)
Oral candidiasis	5 (6)	2 (2)
Sinusitis NOS	4 (5)	2 (2)
Bacteremia	4 (5)	0 (0)
Injury, poisoning and procedural complications		
Transfusion reaction	6 (7)	3 (4)
Abrasion NOS	4 (5)	1 (1)
Investigations		
Cardiac murmur NOS	13 (16)	9 (11)
Blood alkaline phosphatase NOS increased	9 (11)	7 (9)
Aspartate aminotransferase increased	8 (10)	7 (9)
Blood urea increased	8 (10)	1 (1)
Blood lactate dehydrogenase increased	7 (8)	5 (6)
Blood albumin decreased	6 (7)	0 (0)
Blood bicarbonate increased	5 (6)	1 (1)
Blood chloride decreased	5 (6)	1 (1)
Protein total decreased	4 (5)	3 (4)
Blood bicarbonate decreased	4 (5)	1 (1)
Blood bilirubin decreased	4 (5)	1 (1)
Metabolism and nutrition disorders		
Hyperglycemia NOS	27 (33)	16 (20)
Hypoalbuminemia	20 (24)	14 (17)

	Dacogen N = 83 (%)	Supportive Care N = 81 (%)
Hypomagnesemia	20 (24)	6 (7)
Hypokalemia	18 (22)	10 (12)
Hyponatremia	16 (19)	13 (16)
Appetite decreased NOS	13 (16)	12 (15)
Anorexia	13 (16)	8 (10)
Hyperkalemia	11 (13)	3 (4)
Dehydration	5 (6)	4 (5)
Musculoskeletal and connective tissue disorders		
Arthralgia	17 (20)	8 (10)
Pain in limb	16 (19)	8 (10)
Back pain	14 (17)	5 (6)
Chest wall pain	6 (7)	1 (1)
Musculoskeletal discomfort	5 (6)	0 (0)
Myalgia	4 (5)	1 (1)
Nervous system disorders		
Headache	23 (28)	11 (14)
Dizziness	15 (18)	10 (12)
Hypoesthesia	9 (11)	1 (1)
Psychiatric disorders		
Insomnia	23 (28)	11 (14)
Confusional state	10 (12)	3 (4)
Anxiety	9 (11)	8 (10)
Renal and urinary disorders		
Dysuria	5 (6)	3 (4)
Urinary frequency	4 (5)	1 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	33 (40)	25 (31)
Pharyngitis	13 (16)	6 (7)
Crackles lung	12 (14)	1 (1)
Breath sounds decreased	8 (10)	7 (9)
Hypoxia	8 (10)	4 (5)
Rales	7 (8)	2 (2)
Postnasal drip	4 (5)	2 (2)
Skin and subcutaneous tissue disorders		
Ecchymosis	18 (22)	12 (15)
Rash NOS	16 (19)	7 (9)

	Dacogen N = 83 (%)	Supportive Care N = 81 (%)
Erythema	12 (14)	5 (6)
Skin lesion NOS	9 (11)	3 (4)
Pruritis	9 (11)	2 (2)
Alopecia	7 (8)	1 (1)
Urticaria NOS	5 (6)	1 (1)
Swelling face	5 (6)	0 (0)
Vascular disorders		
Petechiae	32 (39)	13 (16)
Pallor	19 (23)	10 (12)
Hypotension NOS	5 (6)	4 (5)
Hematoma NOS	4 (5)	3 (4)

Discussion of Clinically Important Adverse Reactions:

In the Phase 3 trial, the highest incidence of Grade 3 or Grade 4 adverse events in the Dacogen arm were neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%) and leukopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay and discontinuation. Six patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment. (See **PRECAUTIONS**). Of the 83 Dacogen-treated patients, 8 permanently discontinued therapy for adverse events; compared to 1 of 81 patients in the supportive care arm.

No overall difference in safety was detected between patients > 65 years of age and younger patients in these myelodysplasia trials. No significant gender differences in safety or efficacy were detected. Patients with renal or hepatic dysfunction were not studied. Insufficient numbers of non-white patients were available to draw conclusions in these clinical trials.

Serious Adverse Events that occurred in patients receiving Dacogen regardless of causality, not previously reported in **Table 4** include:

Blood and Lymphatic System Disorders: myelosuppression, splenomegaly.

Cardiac Disorders: myocardial infarction, congestive cardiac failure, cardio-respiratory arrest, cardiomyopathy, atrial fibrillation, supraventricular tachycardia.

Gastrointestinal Disorders: gingival pain, upper gastrointestinal hemorrhage.

General Disorders and Administrative Site Conditions: chest pain, asthenia, mucosal inflammation, catheter site hemorrhage.

Hepatobiliary Disorders: cholecystitis.

Infections and Infestations: fungal infection, sepsis, upper respiratory tract infection, bronchopulmonary aspergillosis, peridiverticular abscess, respiratory tract infection, pseudomonal lung infection, Mycobacterium avium complex infection.

Injury, poisoning and procedural complications: post procedural pain, post procedural hemorrhage.

Nervous system disorders: intracranial hemorrhage.

Psychiatric Disorders: mental status changes.

Renal and Urinary Disorders: renal failure, urethral hemorrhage.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, hemoptysis, lung infiltration, pulmonary embolism, respiratory arrest, pulmonary mass.

Allergic Reaction: Hypersensitivity (anaphylactic reaction) to Dacogen has been reported in a Phase 2 trial.

OVERDOSAGE

There is no known antidote for overdosage with Dacogen. Higher doses are associated with increased myelosuppression including prolonged neutropenia and thrombocytopenia. Standard supportive measures should be taken in the event of an overdose.

DOSAGE AND ADMINISTRATION

First Treatment Cycle

The recommended Dacogen dose is 15 mg/m^2 administered by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Patients may be premedicated with standard anti-emetic therapy.

Subsequent Treatment Cycles

The above cycle should be repeated every 6 weeks. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles. Treatment may be continued as long as the patient continues to benefit.

Dose Adjustment or Delay Based on Hematology Laboratory Values

If hematologic recovery (ANC $\geq$ 1,000/μL and platelets $\geq$ 50,000/μL) from a previous Dacogen treatment cycle requires more than 6 weeks, then the next cycle of Dacogen therapy should be delayed and dosing temporarily reduced by following this algorithm:

- Recovery requiring more than 6, but less than 8 weeks - Dacogen dosing to be delayed for up to 2 weeks and the dose temporarily reduced to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy.

- Recovery requiring more than 8, but less than 10 weeks - Patient should be assessed for disease progression (by bone marrow aspirates); in the absence of progression, the Dacogen dose should be delayed up to 2 more weeks and the dose reduced to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy, then maintained or increased in subsequent cycles as clinically indicated.

If any of the following non-hematologic toxicities are present, Dacogen treatment should not be restarted until the toxicity is resolved: 1) serum creatinine $\geq$ 2 mg/dL; 2) SGPT, total bilirubin $\geq$ 2 times ULN; and 3) active or uncontrolled infection.

Use in Geriatric Patients

Geriatric patients were generally dosed at the same level as younger adult patients. Dose adjustments for toxicity should be conducted as specified for the general population.

Preparation of Dacogen

Dacogen is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Dacogen. Please refer to **Handling and Disposal** section.

Dacogen should be aseptically reconstituted with 10 mL of Sterile Water for Injection (USP); upon reconstitution, each mL contains approximately 5.0 mg of decitabine at pH 6.7-7.3. Immediately after reconstitution, the solution should be further diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final drug concentration of 0.1 - 1.0 mg/mL. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C - 8°C) infusion fluids and stored at 2°C - 8°C (36°F 46°F) for up to a maximum of 7 hours until administration.

HOW SUPPLIED

Dacogen™ (decitabine) for Injection is supplied as a sterile lyophilized white to almost white powder, in a single-dose vial, packaged in cartons of 1 vial. Each vial contains 50 mg of decitabine. **(NDC 58063-600-50).**

Storage

Store vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Stability

Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C - 8°C) infusion fluids and stored at 2°C - 8°C (36°F - 46°F) for up to a maximum of 7 hours until administration.

Handling and Disposal

Procedures for proper handling and disposal of antineoplastic drugs should be applied. Several guidances on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

2. National Institutes of Health. Recommendations for the safe handling of cytotoxic drugs. NIH Publication 92-2621. Available at: http://www.nih.gov/od/ors/ds/pubs/cyto/index.htm.

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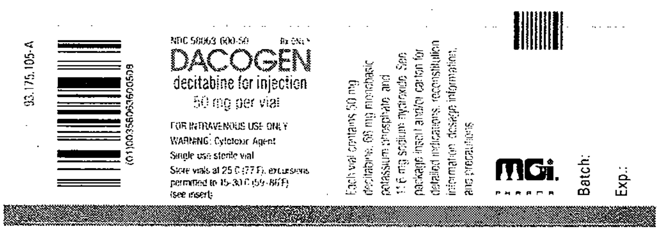
MGI PHARMA, INC.

Manufactured by Pharmachemie B.V. Haarlem, The Netherlands

Manufactured for MGI PHARMA, INC., Bloomington, MN 55437

May 2006

26x85 mm



General information

Item number + version PCH	93.175.105-A
Name product	[illegible] for injection, 50 mg/vial
Lay out	[illegible]
Used colours (+ pantal)	
Afmeting	26x85

Remarks

Authorization

MAC Centre	signature:	....
VV - 1	signature:	....
VV - 2	signature:	....
Label Owner	signature: n.a.	....
Quality Assurance	signature:	....
Purchase Dpt	signature:	....

Modifications

[illegible] 03-02-05

Extra information

PCH 696
afm. 44 x 44 x 90 mm
size: 1,732 x 1,732 x 3,543 inch

DACOGEN
decitabine for injection
50 mg per vial

NDC 58063-600-50

DACOGEN

decitabine for injection

50 mg per vial

FOR INTRAVENOUS USE ONLY

WARNING: Cytotoxic Agent

Single use sterile vial

Rx ONLY

Storage: Store vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) (see insert).

NDC 58063-600-50

See bottom flap for batch number and expiration date.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured by Pharmachemie B.V. Haarlem, The Netherlands

Manufactured for MGI PHARMA, INC. Bloomington, MN 55437

N 3 58063-600-50 8

NDC 58063-600-50

DACOGEN
decitabine for injection
50 mg per vial

FOR INTRAVENOUS USE ONLY

WARNING: Cytotoxic Agent

Single use sterile vial

Rx ONLY

Storage: Store vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) (see insert).

Each vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate, and 11.6 mg sodium hydroxide.

Reconstitution: Aseptically reconstitute with 10 mL of Sterile Water for Injection, USP; each mL will contain 5 mg of decitabine.

Final Concentration: The resultant solution will have a 5 mg per mL (5 mg/mL) concentration and pH of 6.7 to 7.3.

Stability: Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C-8°C) infusion fluids and stored at 2°C-8°C (36°F-46°F) for up to a maximum of 7 hours until administration.

See package insert for detailed indications, reconstitution information, dosage information, and precautions.

93.102.105-A
050503
PCH696
1175/366

batch no.:

exp. date:

Art.nr.: 51.212.255

Production Notes:
456_021_TradePckg

Document size:
Follow Die Line

Trim size:
Follow Die Line

Color(s):
5 color job
C,M,Y,K
Pantone 1935

Bleed(s):
.0625" where needed

LIVE art:
All art is LIVE unless noted.

The color called Non-Print Die Line does not print

General Information

Item number + version PCH	93.102.105-A
Name product	Decitabine for [illegible]
Lay out	Duplex [illegible]
Used colours (+ pantall)	
Afmeting	PCH696 [illegible]

Remarks

Authorization

MAC Centre	signature:
VV 1	signature:
VV 2	signature
Label Owner	signature
Quality Assurance	signature
Purchase Dpt	signature

Modifications

created by EC

Extra information

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/s/

Richard Pazdur
5/2/2006 02:45:58 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-790

MEDICAL REVIEW

Division of Oncology Drug Products
Medical Team Leader's Review

NDA:	21790
Sponsor:	MGI Pharma
Drug Product:	decitabine, Dacogen®
PDUFA Date:	May 26, 2006

Summary:
This reviewer recommends approval of Dacogen (decitabine) for the treatment of patients with myelodysplastic syndrome for all French-British-American (FAB) classifications and intermediate-1, intermediate-2, and high risk populations according to the International Prognostic Scoring System (IPSS).

This review is my second review concerning the data submitted in support of the approval of Dacogen (DAC) for the treatment of patients with myelodysplastic syndrome (MDS). The resubmission was necessary because the Division of Scientific Investigation uncovered discrepancies during their audit between the case report forms, data listings, and patient records for transfusions. Since the transfusion data is crucial for determining whether patients had responded or not, the application could not be approved. Thus an approvable letter was issued on August 31, 2005.

In the approvable letter the Agency recommended that the sponsor consider providing one of the following as a response to their approvable letter:

1. Verify all transfusion data with the source documentation and, based on that data verification, submit an amendment to the NDA revising the study report, CRFs, data listings, and data sets as necessary. Following the resubmission, DSI would inspect these and other study sites; or

2. Submit the results from study EORTC 06011: Phase 3 randomized trial of intravenous low dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.

The Agency sent additional recommendations and comments which were not addressed in this submission for details concerning these please see the approvable letter dated August 30, 2005.

In this resubmission MGI Pharma conducted a data verification plan wherein all transfusions primary source records were reviewed for accuracy and then compared with data listings and data sets. Please see Dr. Kaminskas' review for details. In addition, MGI Pharma reanalyzed the transfusion and response data to conform to the more recently published International working Group criteria. In the originally submitted analysis, patients were transfusion independent if there

was at least one 6-week period in which the patient required no transfusions. In this submission, the transfusion independence definition was modified and increased to an 8-week duration requirement similar to that stated in the IWG criteria. Patients were considered to be transfusion independent on-study if they had a period of at least 56 consecutive days with no transfusions between randomization and study discontinuation.

In this resubmission, the Complete (CR) and Partial Response (PR) rates were unchanged. However, the individual response assessments for 2 patients in the DAC arm were changed. One patient with hematological improvement (HI) was reassessed as having a CR and a second patient originally classified as having a CR was reassessed as having an HI. Two additional patients (1 in each arm) were reclassified as having an HI. Based on the data verification there was a change in the median duration of response from 266 to 288 days for the DAC CR and PR patients. Differences in percentages of patients who were RBC transfusion dependent at baseline and became RBC transfusion independent on study differed between the original study report and the revised study report due to the data verification process and application of the requirement for 8 weeks of transfusion independence.

The sponsor's table below outlines the outcome changes that occurred as a result of the data verification and reanalysis.

Sponsor's Table 3. Summary of Changes in Outcomes (ITT Population)

Various Patient Categories	Dacogen		Supportive Care	
Response	**Original**	**Revised**	**Original**	**Revised**
CR	8	8	0	0
PR	7	7	0	0
HI	11	12	5	6
Median Duration of Response (days)	266	288	NA	NA
Median Duration of Improvement (days)	253	264	212	191
% of patients RBC transfusion dependent at baseline who became independent on study	39%	23%	27%	15%
Change in Response (CR + PR) Response Duration Response Status	8 2		NA	
Change in Improvement (CR + PR + HI) Improvement Duration Improvement Status	16 1		1 1	

The Division of Scientific Investigation conducted a reinspection of two sites based on MGI Pharma's data verification plan and concluded the new data submitted were reliable.

Conclusions and Recommendations:
The results of the data verification and reanalyses did not change the statistically significant difference seen between arms reported in the original submission for Dacogen. For the primary endpoint of response rate, the difference was 17% for DAC compared with 0% for supportive care ($p<0.001$). Based on the response rate, the achievement of transfusion independence and the long duration of responses, this reviewer recommends that Dacogen receive full approval for the treatment of myelodysplastic syndrome (all FAB subtypes and INT-1, INT-2, and high-risk IPSS classification.

In addition, this reviewer would like the sponsor to provide the results of the following study when complete: EORTC 06011 Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy. This request would not be a phase 4 commitment.

The sponsor should also complete the CMC and Clinical Pharmacology and Biopharmaceutics requests in the August 30, 2005 approvable letter.

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/s/

Ann Farrell
3/29/2006 02:12:39 PM
MEDICAL OFFICER

Division Director Summary Review of an NDA Resubmission

NDA: 21-790
Drug: Dacogen™ (decitabine) for Injection
Applicant: MGI PHARMA, Inc.
Date: April 25, 2006

For a summary of the original NDA submission see the Division Director Summary Review of a New Drug Application dated August 27, 2005.

This NDA resubmission seeks approval of Dacogen™ (decitabine) for Injection for the following indication:

> Dacogen is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all 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 IPSS groups.

On August 31, 2005 an approvable letter was issued with the following deficiency:

> The Division of Scientific Investigations (DSI) audited the two sites that accrued the most patients to the major trial (D-0007). These sites were the H. Lee Moffitt Cancer Center and Research Institute in Tampa, FL and the Washington University School of Medicine in St. Louis, MO. When the inspectors compared the source documentation with the case report forms (CRFs) and data listings, they uncovered multiple instances where patients' data were inconsistent. At the Moffitt Cancer Center, 34 patients were enrolled in the study. Of these 34 patients, 12 patient records were inspected. Of these 12 patient records, 6 (50%) had inconsistent data where the source document recorded that the patient had a transfusion and the CRF or data listings did not or the source document did not record a transfusion but the CRF and data listing did. At the Washington University site, similar observations were found, although the frequency appeared to be less. Since the primary endpoint encompassed data on transfusions and the demonstration of decitabine's proposed clinical benefit was the elimination of transfusions, the transfusion data appear too unreliable to be used for an approval decision.

In the letter the applicant was asked to do one of the following:

> 1. Verify all transfusion data with the source documentation and, based on that data verification, submit an amendment to the NDA revising the study report, CRFs, data listings, and data sets as necessary. Following the resubmission, DSI would inspect these and other study sites; or

2. Submit the results from study EORTC 06011: Phase 3 randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.

The applicant chose the first option and resubmitted the application on November 15, 2005. The following is a summary of the resubmitted clinical data.

Safety and efficacy were demonstrated in an open-label, multicenter, randomized, controlled trial in 170 adult patients with all five French-American-British (FAB) subtypes of MDS and with International Prognostic Scoring System scores of High-Risk, Intermediate-2 and Intermediate-1. Eighty-nine patients were randomized to decitabine plus supportive care and 81 were randomized to supportive care. Patients randomized to the decitabine arm received received the drug intravenously at a dose of 15 mg/m^2 over a 3-hour period every 8 hours for 3 consecutive days. This treatment cycle was repeated every 6 weeks, depending on the patient's clinical response and toxicity. Supportive care consisted of blood and blood product transfusions, prophylactic antibiotics, and hematopoietic growth factors.

Responses were classified using the MDS International Working Group criteria. Patients were required to be RBC and platelet transfusion independent during the period of response. The overall response rate (CR+PR) in the intent-to-treat population was 17% in the decitabine-treated group and 0% in the supportive care group ($p<0.001$). In the decitabine-treated group the median duration of response was 288 days and the median time to response was 93 days. All but one of the decitabine-treated patients who responded did so by the fourth cycle. Decitabine treatment did not significantly delay the median time to acute myelogenous leukemia or death.

A total of 164 patients were accrued to two additional open-label, single-arm, multicenter studies of decitabine in patients with any of the FAB subtypes of MDS. The overall response rates in these two studies were 26% (N=66) and 24% (N=98).

The major toxicity of decitabine was myelosuppression as manifested by neutropenia, thrombocytopenia, anemia, and febrile neutropenia. Other common adverse events included nausea, vomiting, diarrhea, constipation, fever, edema, hyperglycemia, hypomagnesemia, hypokalemia, arthralgias, back pain, cough, headache, insomnia, rash, petechiae, and pallor.

Clinical and Statistical Review

The combined Clinical and Statistical Review of the resubmission made the following recommendation on regulatory action.

1. Approval of decitabine for treatment of patients with myelodysplastic syndrome (MDS). The approval is recommended on the basis of a Complete Response by the sponsor to the approvable letter by the Agency. On the basis of a positive report by the Division of Scientific Investigations on the inspections of study sites (see below in 4.4 Data Quality and Integrity), the remonitored and verified data by the sponsor supports the efficacy and safety of decitabine in MDS...

2. Decitabine is an inhibitor of DNA methylation, promoting differentiation of hematopoietic cells, and is also a cytotoxic agent causing cell cycle arrest and apoptosis. It is effective in about 17% to 26% of MDS patients in completely or partially restoring normal blood cell counts and normal percentage of blasts in the bone marrow, and in reducing or eliminating transfusion dependence. The therapeutic effects are generally long lasting (median durations of response were 146 to 288 days). Decitabine treatment has not been shown to result in survival benefit. Responses to decitabine have been shown to occur in patients with all FAB subtypes, with high-risk, intermediate-2, and intermediate-1 IPSS subtypes, in previously treated as well as untreated patients, and in patients with de novo or secondary MDS.

3. The dose of decitabine is 15 mg/m^2 administered intravenously over 3 hours; this dose is repeated every 8 hours for 3 days every six weeks. The dose is adjusted according to blood cell counts. Patients should be treated for a minimum of four 6-week cycles. A complete or partial response may take longer than 4 cycles. Treatment may be continued for as long as the patient continues to benefit.

The review provided the following summary of the data quality and integrity.

During the first review cycle, the Agency's Division of Scientific Investigations audited the 2 largest sites of patient enrollment in the randomized D-0007 trial. These were Moffitt Cancer Center in Tampa, FL and Washington University in St. Louis, MO. The FDA investigators concluded that data from both sites are unreliable. The key issue was the accuracy of transfusion data, since response rates and clinical benefit hinge on these data.

Following an Approvable Letter from the FDA on September 1, 2005, the Sponsor initiated a Data Verification Plan to review and record all transfusion information for all patients (N=170) at all 23 sites in the D0007 phase 3 controlled trial. Site medical records (hospital and clinic), and all available medical records from referring or collaborating medical facilities, site blood bank transfusion records, available off-site transfusion records and other available source documentation were reviewed at each of these sites for each patient. New case report form (CRF) pages specific to transfusion data were completed, and forwarded to the Sponsor's Clinical Operations group, where they were compiled for analysis. An independent assessor reviewed and verified all transfusion

records. The Sponsor resubmitted the NDA with all changes resulting from the Data Verification Report for a second review cycle.

The Division requested the Division of Scientific Investigations to audit 2 sites, one previously inspected (Moffitt Cancer Center in Tampa, FL) and one not previously inspected (Rush Cancer Institute, Rush-Presbyterian St. Luke's Medical Center, Chicago, IL).

The inspection at Moffitt Cancer Center involved review of previously inspected records of 6 subjects and of 5 subjects' records that had not been previously reviewed. The inspector's assessment of data integrity was that the transfusion data from this site are now reliable.

The inspection at Rush-Presbyterian St. Luke's center involved records reviews of 7 of the 20 subjects enrolled in the D-0007 trial. The inspector issued a Form FDA 483 citing 4 major inspectional observations relating to patients' assessments (especially missing Quality of Life assessments), failures to report SAEs within 24 hours to the IRB, failures in the maintenance of adequate and accurate case histories, including source documentation of off-site blood transfusion records for on-site review, and failure to obtain signed informed consents from two subjects. However, the inspector's assessment of the integrity of the primary efficacy data is that the data from this site are reliable.

The review had the following Phase 4 study suggestions.

- Completion of EORTC 06011 Phase 3 randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.
- Metabolism of decitabine, in particular whether any of the cytochrome P450 enzymes is involved in the biotransformation of decitabine,
- Pharmacokinetics and safety of decitabine in patients with mild hepatic impairment, and
- Pharmacokinetics and safety of decitabine in patients with mild to moderate renal impairment.
- Dosing regimens that are at least as effective as the present one, and can be administered without a three day hospitalization.

Medical Team Leader Review

The review of the resubmission by Dr. Ann Farrell had the following conclusions and recommendations.

The results of the data verification and reanalyses did not change the statistically significant difference seen between arms reported in the original submission for Dacogen. For the primary endpoint of response rate, the difference was 17% for

DAC compared with 0% for supportive care ($p<0.001$). Based on the response rate, the achievement of transfusion independence and the long duration of responses, this reviewer recommends that Dacogen receive full approval for the treatment of myelodysplastic syndrome (all FAB subtypes and INT-1, INT-2, and high-risk IPSS classification.

In addition, this reviewer would like the sponsor to provide the results of the following study when complete: EORTC 06011 Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy. This request would not be a phase 4 commitment.

The sponsor should also complete the CMC and Clinical Pharmacology and Biopharmaceutics requests in the August 30, 2005 approvable letter.

Clinical Inspection Summary

The Clinical Inspection Summary of March 7, 2006 provided the following overall assessment of findings and general recommendations.

The sites inspected, that of Dr. Hussain and Dr. Gregory, were found to generally adhere to the applicable regulations governing the conduct of clinical investigations; with noteworthy observations cited on a Form FDA 483 for Dr. Gregory's sight. Those observations revealed that while the study was active and under the responsible control of Dr. Azra Raza, the former CI, numerous protocol violations were noted that included but were not limited to missing several protocol-required primary efficacy endpoint supporting measurements and a number of required measurements for determining secondary endpoint measurements, in particular quality of life. These observations, of the conduct of the study under CI Dr. Azra Raza, while reflecting poorly on the management of study protocol adherence and safety and monitoring activities should not grossly impact the reliability of primary efficacy data submitted to the agency in support of NDA 21790/000. However, quality of life measurements, a secondary efficacy measurement, should be considered unreliable for the data produced by study site #1046 under the CI Dr. Azra Raza, Rush Cancer Institute, Chicago, IL.

Sponsor monitoring and oversight activities of the study D-0007 appeared to have been inadequate. The reported protocol violations found on FDA inspection, poor protocol adherence reported in this clinical inspection summary and poor record keeping in particular with respect to source documentation to support CRF transfusion history's per study subject (reference: DSI reviewer Mary Mease Clinical Inspection Summary dated July 28, 2005) could have been detected and corrected by oversight and monitoring by the sponsor. The findings and observations reported here and those reported in the DSI Clinical Inspection Summary dated July 28, 2005 suggest that the agency should consider re-

evaluation of these observations and their impact on data validity and integrity each time data from study D-0007 is proposed to be used to support any post-marketing FDA actions regarding safety or efficacy...

Clinical Pharmacology and Biopharmaceutics Review

The review of the resubmission by Roshi Ramchandani, Ph.D. had the following conclusion and recommendation.

> The Office of Clinical Pharmacology (OCP) has reviewed the Clinical Pharmacology section of NDA 21-790 and finds it to be acceptable, with the following recommendations:
>
> - We recommend that you conduct in vitro studies in human hepatic microsomes to evaluate if decitabine inhibits CYP2C8.

DMETS Consultation

The DMETS Consultation of March 6, 2006 found the proprietary name to be acceptable and identified deficiencies in the package insert, carton labeling, and container label. These were communicated to the applicant and were addressed in the CMC review below.

Chemistry, Manufacturing and Controls Review

The CMC Review by Josephine Jee had the following recommendation and conclusion on approvability.

> Manufacturing and Controls (CMC). The deficiencies identified in Review No. 1 and Review No. 2 related to the drug substance and drug product have been addressed by the applicant. In addition, deficiencies identified in the package labeling insert, carton label and container label have been addressed on 23-MAR-2006.
>
> J. Barletta, Ph.D. also recommended for approval on 15-JUL-2005 from the standpoint of Microbiology.
>
> All outstanding issues on carton and container and package insert labeling have been adequately addressed in the amendment dated 23-MAR-2006.

DDMAC Consult

The February 1, 2006 DDMAC Consult by Joseph Grillo and Iris Masucci provided comments on the draft labeling which were considered during the labeling meetings.

Conclusions and Recommendation

I concur with the recommendations for approval of the application. The applicant has verified the transfusion data and the efficacy results have not changed significantly. DSI inspected two study sites during this review cycle and concluded that while there were a number of noteworthy findings at Dr. Gregory's site, they "should not grossly impact the reliability of primary efficacy data submitted to the agency in support of NDA 21790/000." I agree that no phase 4 studies are required and that the suggestions for phase 4 studies should be communicated to the applicant.

Robert L. Justice, M.D., M.S.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Robert Justice
4/25/2006 02:26:45 PM
MEDICAL OFFICER

CLINICAL AND STATISTICAL REVIEW

Application Type	NDA
Submission Number	21-790 SN-000
Submission Code	AZ, SU
Letter Dates	November 14 & 18, 2005
Stamp Dates	November 15 & 21, 2005
PDUFA Goal Date	May 15, 2006
Reviewer Name	Edvardas Kaminskas, M.D., Kun He, Ph.D.
Review Completion Date	March 29, 2006
Established Name	Decitabine
Proposed Trade Name	Dacogen™
Therapeutic Class	Antineoplastic
Applicant	Supergen
Priority Designation	S
Formulation	Lyophilized Powder
Dosing Regimen	Intravenous
Indication	Myelodysplastic syndrome
Intended Population	Adults

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

1. Approval of decitabine for treatment of patients with myelodysplastic syndrome (MDS). The approval is recommended on the basis of a Complete Response by the sponsor to the approvable letter by the Agency. On the basis of a positive report by the Division of Scientific Investigations on the inspections of study sites (see below in 4.4 Data Quality and Integrity), the remonitored and verified data by the sponsor supports the efficacy and safety of decitabine in MDS. This review will largely be concerned with sections in which there are changes from the original review filed in DFS on August 29, 2005. Sections in which there are no changes are either copied from the original review (for ease in following the review), or referenced to the original review.

2. Decitabine is an inhibitor of DNA methylation, promoting differentiation of hematopoietic cells, and is also a cytotoxic agent causing cell cycle arrest and apoptosis. It is effective in about 17% to 26% of MDS patients in completely or partially restoring normal blood cell counts and normal percentage of blasts in the bone marrow, and in reducing or eliminating transfusion dependence. The therapeutic effects are generally long lasting (median durations of response were 146 to 288 days). Decitabine treatment has not been shown to result in survival benefit. Responses to decitabine have been shown to occur in patients with all FAB subtypes, with high-risk, intermediate-2, and intermediate-1 IPSS subtypes, in previously treated as well as untreated patients, and in patients with *de novo* or secondary MDS.

3. The dose of decitabine is 15 mg/m^2 administered intravenously over 3 hours; this dose is repeated every 8 hours for 3 days every six weeks. The dose is adjusted according to blood cell counts. Patients should be treated for a minimum of four 6-week cycles. A complete or partial response may take longer than 4 cycles. Treatment may be continued for as long as the patient continues to benefit.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Standard procedures for adverse event reporting.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

The following Phase 4 suggestions should be communicated to the applicant:

- Completion of EORTC 06011 Phase 3 randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS

or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.

- Metabolism of decitabine, in particular whether any of the cytochrome P450 enzymes is involved in the biotransformation of decitabine,
- Pharmacokinetics and safety of decitabine in patients with mild hepatic impairment, and
- Pharmacokinetics and safety of decitabine in patients with mild to moderate renal impairment.
- Dosing regimens that are at least as effective as the present one, and can be administered without a three day hospitalization.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Product name, class, starting dose and route of administration: Dacogen™ for Injection (DAC) contains decitabine, an analogue of the natural deoxyribonucleoside 2'-deoxycytidine. Decitabine promotes cell differentiation and is also cytotoxic. DAC is administered by a 3-hour intravenous infusion at a starting dose of 15 mg/m^2 every 8 hours for three days every 6 weeks.
Indications and populations studied: Adult patients with all FAB subtypes and with high-risk, intermediate-2 and intermediate-1 IPSS categories of myelodysplastic syndrome.
Number of pivotal efficacy and safety trials: One phase 3 controlled trial, supported by two single-arm phase 2 trials.
Number of patients enrolled in the primary trials: 170 in the phase 3 trial and 164 in the phase 2 trials.
Overall number of patients in the safety database and extent of exposure: 240 patients in the three primary studies and 183 patients in six ongoing studies. In the phase 3 controlled trial, the average dose per treatment cycle was 247 mg, median number of cycles was 4, and the median cumulative dose received was 735 mg (range, 203 - 2614 mg).

1.3.2 Efficacy

Efficacy of DAC in treatment of MDS is demonstrated in the supportive care-controlled, randomized phase 3 trial D-0007. In this trial 89 patients were randomized to DAC and 81 patients to supportive care (SC). Of the 89 patients randomized to DAC, 83 were treated with DAC. Of the 81 patients randomized to SC, 3 patients crossed over to the DAC arm. Similar efficacy results were found in the two single arm, multicenter phase 2 studies, PCH 95-11 and PCH 97-19, in which 66 patients and 98 patients, respectively, were treated with DAC. All three trials had enrolled patients with MDS of all FAB subtypes and of high-risk, intermediate-2 (INT-2) and intermediate-1 (INT-1) IPSS categories.

Endpoints: There were two primary endpoints in the controlled trial, overall response rate (complete or partial) and time to progression to acute myeloid leukemia or death. Secondary endpoints included survival, transfusion requirements, overall response rate plus the rate of hematological improvement (a lesser response than partial response), quality of life measures,

and cytogenetic response. The primary endpoints in both phase 2 studies were best hematological response (defined as complete remission, partial remission, improvement, stable disease, relapse, or progression), transfusion requirements, and changes in performance status.

Endpoint issues:

- The sponsor initially proposed overall response rate as the primary endpoint for the controlled trial, while the Agency suggested time to progression to AML or death. Both became co-primary endpoints. The possibility of achieving a statistically significant delay in time to progression to AML or death with DAC treatment was suggested by the CALGB 9221 trial in which MDS patients were treated with azacitidine, an agent with a similar mechanism of action. A later statistical analysis of this trial by the Agency concluded that such a delay was not demonstrated. Thus, there is so far no evidence that any agent is effective in prolonging the time to progression to AML or death in MDS patients.

- The definitions of overall response rates differ between the pivotal controlled trial and the phase II studies, as criteria for response rates changed with publications by international working groups. The main difference is that a complete or partial response by the later criteria needs to be maintained for at least 8 weeks, while the earlier criteria have no such requirement.

Efficacy Conclusions:

- Patients treated with DAC had an overall response rate of about 17% (in ITT population) as compared to no responses in the SC patients. This difference was statistically significant ($p < 0.001$). DAC-treated patients in the single-arm studies had overall response rates of 24% and 26% (ITT populations).
- Time to progression to AML or death was not significantly different in DAC-treated patients from that in SC patients ($p=0.160$).
- The clinical benefit of DAC-induced responses was normalization of blood counts and bone marrow blast percentages and elimination of the need for transfusions in patients who were transfusion-dependent at baseline.
- The responses were long-lasting. The median durations of responses were 288 days, 146 days, and 250 days in the controlled trial D-0007, PCH 97-19 study, and PCH 95-11 study, respectively. The median time to response in the controlled trial was 93 days.
- Subgroup analyses revealed:
    - Patients with MDS of all FAB subtypes and IPSS classifications had approximately similar response rates.
    - Patients of all age ranges had similar response rates.
    - Female patients had twice the response rates of male patients in two of the studies, and about the same response rate as male patients in the third study. This reviewer, in light of similar response rates in female and male MDS patients in the azacitidine trials, is not convinced that there is gender difference in response rate to DAC.

  - Response rates were not analyzed by race/ethnicity, because more than 90% of the subjects were White.
  - Responses occurred in patients with or without prior therapy for MDS and in patients with *de novo* and with secondary MDS, although there were too few patients with secondary MDS or with prior therapy for MDS to make comparisons of response rates.
- Analyses of secondary endpoints revealed:
  - DAC treatment resulted in decreased RBC and platelet transfusion requirements in transfusion-dependent patients, and decreased the risk of patients becoming transfusion-dependent.
  - Febrile neutropenia occurred more frequently in DAC-treated patients than in supportive care patients.
  - Hematological Improvement rates (Complete Response plus Partial Response plus Hematological Improvement) were higher in DAC-treated patients than in supportive group patients.
  - In Quality of Life analyses, DAC-treated patients had statistically superior global health status, less dyspnea and less fatigue.
  - About 19% (9/48) of patients with clonal abnormalities at baseline) had a major cytogenetic response (no remaining abnormality) and 2% (1/48) had a minor cytogenetic response (≥ 50% reduction in abnormal metaphases) in the DAC treatment arm. About one-half (8/15) of patients who had a CR or PR had a major cytogenetic response. About 6% (2/33) of patients in the SC arm had a major cytogenetic response.

Dosage regimen is appropriate, since controlled trial patients received 97% of the prescribed dose. Delays of treatment and dose reductions in subsequent cycles occurred in about one-third of patients.

Role in armamentarium: The efficacy of DAC in MDS is similar to that of azacitidine as measured by response rate.

1.3.3 Safety

- A total of 240 patients with MDS received DAC at the same dose as specified in the NDA in the three primary studies. DAC was administered in cycles of 6 weeks, and the median number of cycles was 3, with some patients receiving up to 9 cycles.
- There were no deaths that were attributed to DAC toxicity, although thrombocytopenia aggravated by DAC treatment may have contributed to bleeding, including intracerebral hemorrhage. The number of deaths was greater in the supportive care arm than in the DAC treatment arm during the study period; however, the total number of deaths during the total observation period was about the same in both arms. Disease progression to AML and infection were the most common causes of death in both arms.
- Hematological adverse events (neutropenia, febrile neutropenia, thrombocytopenia, anemia and leukopenia) were prominently more common in the DAC arm than in the SC arm. Hematological adverse events did not decrease with successive cycles unless the

patient had a response. Gastrointestinal disorders (nausea, constipation, diarrhea, vomiting, abdominal pain, stomatitis, dyspepsia and ascites) were more common in the DAC arm than in the supportive care arm. They decreased after the first two cycles of DAC therapy with appropriate medications. Fever, bacterial and fungal infections, painful joints or muscles, backaches, chest wall discomfort, headache, insomnia, confusional state, ecchymoses, pallor, erythemas, alopecias and skin disorders were also more common in the DAC arm than in the SC arm. There were no greater than grade 2 hepatic or renal function abnormalities. Vital signs reflected general clinical condition rather than MDS or DAC therapy.

- Adverse events (thrombocytopenia, lymphadenopathy, neutropenia, pneumonia, *M. avium* infection, cardiac arrest, and elevated liver function tests) led to discontinuation of DAC therapy in 10% of patients, and of withdrawal from the supportive care arm in 2% of patients (because of COPD and of dyspnea). About 19% of patients had dose delays, about 5% of patients had dose reduction, and about 11% of patients had dose reduction and dose delay.
- There are no safety data on pregnant or lactating women (who were excluded from enrollment), or on infants and children (MDS is very rare in childhood) in this submission.
- Overdose data is available from older studies in which patients were treated with several-fold higher DAC dosages. The main toxicity was hematological.
- The most common adverse events due to DAC overlap those of MDS, making attribution and safety evaluation difficult. DAC therapy is effective in eliminating or reducing transfusion dependence, and the adverse events appear to be tolerable for the achievement of this goal.

1.3.4 Dosing Regimen and Administration

DAC is administered by a 3-hour intravenous infusion at a starting dose of 15 mg/m^2 every 8 hours for three days every 6 weeks.

1.3.5 Drug-Drug Interactions

Severe thrombocytopenia was reported in a patient receiving DAC and tamoxifen with bleeding and subdural hematoma. Antineoplastic agents appear to accentuate tamoxifen-associated thrombocytopenia, which has been reported with tamoxifen monotherapy as well.

1.3.6 Special Populations

There is no information on patients with hepatic or renal impairment because they were excluded from the trials. There is limited information on patients of different races/ethnic backgrounds other than White.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

- Dacogen™ for Injection contains 5-aza-2'-deoxycytidine or decitabine (abbreviated as DAC in the rest of the review), an analogue of the natural deoxyribonucleoside 2'-deoxycytidine. In 5-aza-2'deoxycytidine the carbon at position 5 of the pyrimidine ring is replaced by a nitrogen (see Figure 1 below).
- Dacogen™ for Injection is a white sterile lyophilized powder supplied in a clear colorless glass vial. Each vial contains 50 mg decitabine, potassium dihydrogen phosphate and sodium hydroxide. It is to be reconstituted with 10 mL of Sterile Water for Injection and then further diluted with 5% D/W, NS, or Lactated Ringer's for intravenous (IV) infusion. The final drug concentration is to be 0.1 – 1.0 mg/mL.
- The generic name is decitabine.
- The chemical name is 4-amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one.
- Proposed trade name is Dacogen™.

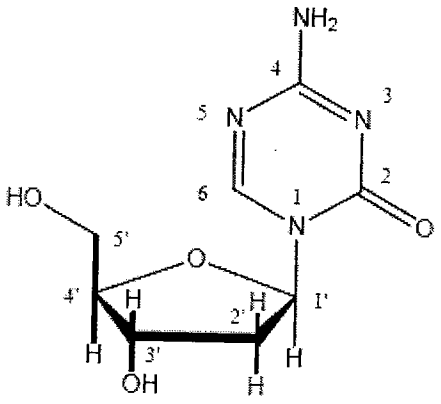


Figure 1. Decitabine

- It is a new molecular entity (NME).
- Pharmacologic class: DAC is an antineoplastic agent. It is incorporated into DNA following phosphorylation to 5-aza-dCTP and is a specific inhibitor of the DNA methyltransferase enzymes. DNA methylation occurs after DNA replication and involves the transfer of a methyl group from S-adenosyl-methionine to the position 5 of the deoxycytidine residues. These reactions are carried out by DNA-methyltransferases I, IIIa and IIIb. Decitabine is able to inhibit DNA methylation by the formation of a stable complex between the DNA methyltransferase enzymes and 5-aza-cytosine-substituted DNA. In general, methylation of DNA represses gene expression, whereas demethylation

results in gene activation. In mammalian cells, about 5% of the doxycytidine residues in DNA are present as 5-methyldeoxycytidine. By inhibiting DNA methylation, DAC prevents DNA hypermethylation of CpG islands, which is associated with a variety of tumors and MDS. By hypomethylation of replicating DNA, DAC induces neoplastic cell differentiation into normal cells. DAC also causes cell cycle arrest and apoptosis. Thus, it is both a cell differentiation inducing agent and a cytotoxic agent.

- Indication for DAC is treatment of patients with myelodysplastic syndrome (MDS) including previously treated and untreated, *de novo* and secondary. The recommended dosing regimen is 15 mg/m^2 administered by continuous IV infusion over 3 hours repeated every 8 hours for 3 days every 6 weeks. Age restriction is not specified.

2.2 Currently Available Treatment for Indications

Vidaza™ (5-azacitidine) was approved on May 19, 2004 for a similar indication. The mechanisms of action of 5-azacitidine and of decitabine on the inhibition of DNA methylation are thought to be identical.

2.3 Availability of Proposed Active Ingredient in the United States

The product is not currently marketed in this country.

2.4 Important Issues with Pharmacologically Related Products

The pathophysiology of MDS overlaps to a great extent the most common toxicities of azacitidine and DAC, which result from myelosuppression. Consequently, anemia, leukopenia, neutropenia, infections, thrombocytopenia, bleeding, hematomas and patechiae are common events with MDS and with treatment with azacitidine and DAC. Gastrointestinal adverse events, such as anorexia, nausea, vomiting, diarrhea, and constipation are common during treatment with azacitidine and DAC. Transient elevations of hepatic enzymes are common to both agents. Hepatic failure may develop in patients with pre-existing hepatic disease.
Overall response rates are approximately the same with DAC and azacitidine.

2.5 Presubmission Regulatory Activity

See original review filed on August 29, 2005.

2.6 Other Relevant Background Information

See original review filed on August 29, 2005.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See original review filed on August 29, 2005.

3.2 Animal Pharmacology/Toxicology

See original review filed on August 29, 2005.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

See original review filed on August 29, 2005.

4.2 Tables of Clinical Studies

See original review filed on August 29, 2005.

4.3 Review Strategy

See original review filed on August 29, 2005.

4.4 Data Quality and Integrity

During the first review cycle, the Agency's Division of Scientific Investigations audited the 2 largest sites of patient enrollment in the randomized D-0007 trial. These were Moffitt Cancer Center in Tampa, FL and Washington University in St. Louis, MO. The FDA investigators concluded that data from both sites are unreliable. The key issue was the accuracy of transfusion data, since response rates and clinical benefit hinge on these data.

Following an Approvable Letter from the FDA on September 1, 2005, the Sponsor initiated a Data Verification Plan to review and record all transfusion information for all patients (N=170) at all 23 sites in the D0007 phase 3 controlled trial. Site medical records (hospital and clinic), and all available medical records from referring or collaborating medical facilities, site blood bank transfusion records, available off-site transfusion records and other available source documentation were reviewed at each of these sites for each patient. New case report form (CRF) pages specific to transfusion data were completed, and forwarded to the Sponsor's Clinical Operations group, where they were compiled for analysis. An independent assessor reviewed and verified all transfusion records. The Sponsor resubmitted the NDA with all changes resulting from the Data Verification Report for a second review cycle.

The Division requested the Division of Scientific Investigations to audit 2 sites, one previously inspected (Moffitt Cancer Center in Tampa, FL) and one not previously inspected (Rush Cancer Institute, Rush-Presbyterian St. Luke's Medical Center, Chicago, IL).

The inspection at Moffitt Cancer Center involved review of previously inspected records of 6 subjects and of 5 subjects' records that had not been previously reviewed. The inspector's assessment of data integrity was that the transfusion data from this site are now reliable.

The inspection at Rush-Presbyterian St. Luke's center involved records reviews of 7 of the 20 subjects enrolled in the D-0007 trial. The inspector issued a Form FDA 483 citing 4 major inspectional observations relating to patients' assessments (especially missing Quality of Life assessments), failures to report SAEs within 24 hours to the IRB, failures in the maintenance of adequate and accurate case histories, including source documentation of off-site blood transfusion records for on-site review, and failure to obtain signed informed consents from two subjects. However, the inspector's assessment of the integrity of the primary efficacy data is that the data from this site are reliable.

4.5 Compliance with Good Clinical Practices

See original review filed on August 29, 2005.

4.6 Financial Disclosures

See original review filed on August 29, 2005.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

See original review filed on August 29, 2005.

5.2 Pharmacodynamics

See original review filed on August 29, 2005.

5.3 Exposure-Response Relationships

See original review filed on August 29, 2005.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor proposed the following indication: Decitabine is indicated for treatment of patients with myelodysplastic syndrome (MDS), including previously treated and untreated, *de novo* and secondary MDS, of the following subtypes:

- By FAB classification: refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.

- By IPSS classification: High Risk, INT-2, and INT-1.

The revised indication as shown in the Labeling Review (section 10.1) is:

Dacogen is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all 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 IPSS groups.

6.1.1 Methods

See original review filed on August 29, 2005. Only the results of the phase 3 controlled trial will be described. The results of the single-arm phase 2 trials are not changed from the original review filed on August 29, 2005.

As a result of the Data Verification process described above, the definition of transfusion independence was changed. In the original analysis, patients were considered to be transfusion independent if there was at least one fixed 6-week period in which the patient required no transfusions. In the reanalysis, the definition of transfusion independence was modified to the 8-week duration requirement stated in the International Working Group criteria. Patients were considered to be transfusion independent on-study if they had a period of at least 56 consecutive days with no transfusions between randomization and study discontinuation.

6.1.2 General Discussion of Endpoints

The phase 3 controlled trial (D-0007) was the major source of data for the efficacy review. The single-arm trials and literature reports were used to support the results of the controlled trial.

Patients in the controlled trial consisted of all 5 FAB subgroups and of High-risk, Intermediate-2 (INT-2) and Intermediate-1 (INT-1) subgroups of the IPSS classification.

Study Objectives.

- The overall objective of this multi-center study was to demonstrate the superiority of DAC injection over SC for treatment of adults with MDS.
- The secondary objectives included
  - Overall survival
  - Transfusion requirements
  - Rates of febrile neutropenia
  - Percent of patients achieving Hematological Improvement (CR + PR + HI)
  - Quality of Life
  - Cytogenetic Responses and Safety.

Primary endpoint: The co-primary endpoints were

- Overall Response Rate (CR + PR) as defined by the MDS International Working Group criteria, and
- Time to AML or Death.

Secondary endpoints:

- Survival
- Transfusion Requirements
- Improvement (CR + PR + Hematological Improvement)
- Quality of Life, and
- Cytogenetic Response.

6.1.3 Study Design

The study design of the controlled D-0007 trial meets the regulation on adequate and well-controlled studies (21 CFR 314.126) and the results provide a reasonable assessment of benefit.

This was an open-label, parallel-group, randomized trial of 170 adult patients with histologically confirmed MDS who met IPSS criteria for INT-2 or high-risk categories, and later, as allowed by Protocol Amendment 3, patients meeting the INT-1 risk category.

Given that DAC is administered IV every 8 hours for 3 days, a double-blind study was not possible. A blinded review of all bone marrow aspirates and biopsies was performed by an expert hematopathologist.

Study Entry Procedures

- Baseline history, physical examination, bone marrow aspirates, biopsies, and cytogenetics samples, CBC, serum chemistries, serum hCG, and the EORTC Quality of Life questionnaire completed.
- Randomization to DAC or SC treatment arms was 1:1 using a centralized, call-in randomization process. The Biometrics and Statistics Department of SuperGen

supervised each randomization. Patients were stratified by study center, IPSS classification and type of MDS (*de novo* or secondary).

- Baseline Demographics and Other Patient Characteristics are shown in Reviewer's Table 1 (data from Sponsor's Table 7) below in Selection of Study Population (6.1.2.5 in the submission).

Treatment Procedures

- Both treatment groups received standard supportive care, including PRBC or platelet transfusions, erythropoietin, thrombopoietin, prophylactic antibiotics, and hospitalization.
- Patients in the DAC arm received DAC 15 mg/m^2 injection as nine 3-hour infusions over 3 days (one infusion every 8 hours for 3 days) per 6-week cycle administered in the hospital, clinic or through home infusion care.
- Selection of doses: The dose and schedule in the 3 trials submitted in this NDA was derived from a phase 1/2 dose-escalation study in 38 patients with AML, CML or MDS (PCH 88-01). The subsequent phase 2 studies (PCH 95-11 and PCH 97-19) used the lowest dose level in MDS patients (15 mg/m^2 administered over 4 hours every 8 hours for 3 days) in PCH 88-01 to reduce myelotoxicity and to allow for bone marrow recovery.
- Every 6 weeks patients received a medical H & P, CBC, serum chemistries, and Q of L questionnaire. Cycles were repeated once the patient's hematologic parameters returned to pretreatment or to normal levels.
- Criteria for dose reduction or cycle delay: If blood count recovery took > 6 weeks, but < 8 weeks, DAC was held for up to 2 weeks and the dose was reduced to 11 mg/m^2 every 8 hours; if blood count recovery took > 8 weeks but <10 weeks, patient was assessed for disease progression by bone marrow aspirate; if there was no progression, DAC was held for 2 more weeks and the dose was reduced as above. If the following non-hematological toxicities occurred, DAC treatment was not restarted until the toxicity resolved: serum creatinine > 2 mg/dL, SGPT, serum bilirubin > 2 x ULN, or active uncontrolled infection.
- Every 12 weeks a BM aspirate and biopsy were performed to evaluate response to treatment. After any 2 cycles, DAC arm patients were taken off study if they demonstrated progressive disease (PD), as defined by the MDS International Working Group. Other patients were continued on treatment for a maximum of 10 cycles.
- At the end of study, the final bone marrow aspirate and biopsy, CBC, serum chemistries, and hCG were obtained, and Q of L questionnaire was administered.
- Crossover: Patients in the SC arm who progressed to AML or experienced rapidly progressive disease were initially allowed to cross over and receive DAC. This practice was stopped with Amendment 2 (by that time 3 patients had crossed over). Subsequently, such patients were permitted to participate in a different phase 2 protocol of DAC for AML.
- Selection bias was minimized by a centralized all-in randomization process.
- Evaluation bias was limited by the use of a blinded central review of all bone marrow aspirates and biopsies in addition to the initial diagnoses by local pathologists. (The inter-pathologist concordance in hematologic classification of MDS is 67%).

Selection of Study Population

Inclusion Criteria:

- Diagnosis of MDS (*de novo* or secondary) of any of 5 FAB classifications and IPSS >0.5, as determined by CBC, bone marrow assessment, and cytogenetics within 30 days of randomization.
- 18 years or older
- ECOG or WHO PS of 0 – 2
- Signed informed consent
- Adequate renal and hepatic function (creatinine ≤ 1.5 mg/dL, bilirubin ≤ 1.5 mg/dL, SGPT ≤ 2 x ULN)
- Not pregnant, adequate pregnancy prevention, not lactating.

Exclusion Criteria:

- AML or other progressive malignant disease
- Treatment with danazol, androgenic hormones, or colony-stimulating factors within 7 days of start of study
- Any investigational agent within 30 days prior start of study
- Uncontrolled cardiac disease, CHF, uncontrolled restrictive or obstructive pulmonary disease
- Active viral or bacterial infection
- Concurrent autoimmune hemolytic anemia or thrombocytopenia
- HIV serology
- Mental illness
- Not recovered from prior therapy toxicity; been off all chemotherapy for less than 4 weeks (6 weeks for nitrosoureas and BMT)

Removal of Patients from Therapy or Assessments:

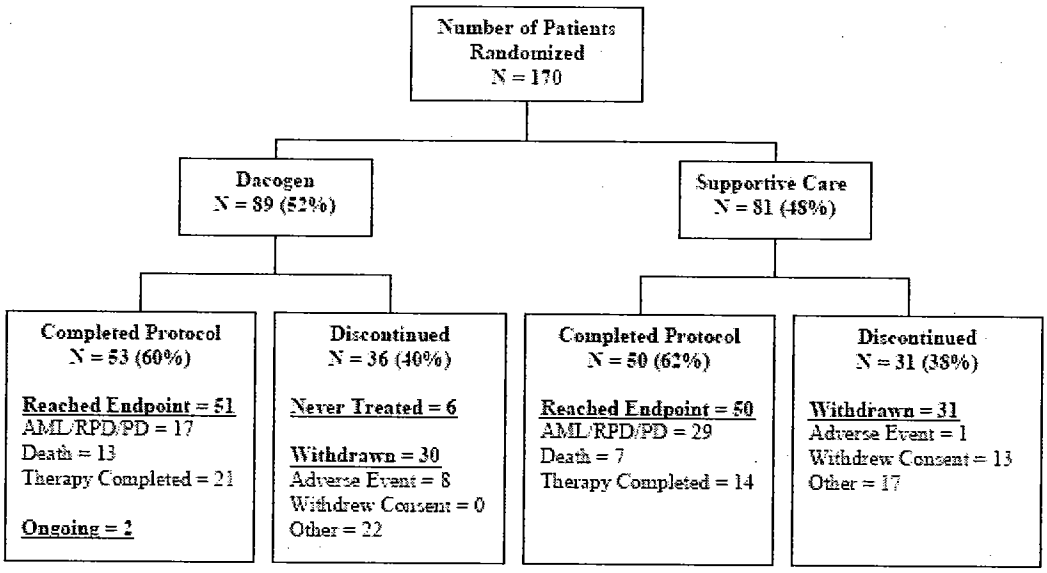
- Evidence of disease progression, per protocol, at any time during the study
- Transformation to AML
- Failure to achieve PR after 6 cycles of DAC
- Failure to achieve CR after 8 cycles of DAC
- Any CTC Grade 4 (life-threatening) non-hematological toxicity; or any Grade 3 (severe) non-hematological toxicity failing to improve within 10 weeks following a DAC treatment cycle
- Failure to recover from prolonged cytopenia within 10 weeks after administration of a reduced dose of DAC
- Patient's request to end study treatment
- Patient withdrawal of informed consent
- SC patients that progressed to AML or had rapid progression of disease qualified for AML protocol

Study Population: Demographic and Other Baseline Characteristics randomized to the two study arms are shown in Reviewer's Table 1 below (from Sponsor's Table 7).

Reviewer's Table 1. Baseline Demographics and Other Baseline Characteristics

Demographic or Other Patient Characteristic	**Decitabine, N = 89**	**Supportive Care, N = 81**
Age, mean, median and (range) in years	69, 70 (31 – 85)	67, 70 (30 – 82)
Age stratification		
< 65 years (%)	23 (26%)	30 (37%)
65 – 74 (%)	42 (47%)	35 (43%)
75 - (%)	24 (27%)	16 (20%)
Gender : Male	59 (66%)	57 (70%)
Female	30 (34%)	24 (30%)
Race: White	83 (93%)	76 (94%)
Afro-American	4 (4%)	2 (2%)
Other	2 (2%)	3 (4%)
Weeks since MDS diagnosis		
Mean	86	77
Median	29	35
Range	2 – 667	2 – 865
Percent Blasts in BM		
Mean	11%	11%
Median	10%	9%
Range	[redacted]	[redacted]
Missing values	[redacted]	[redacted]
Type of MDS		
De novo MDS	77 (87%)	70 (86%)
Secondary MDS	12 (13%)	11 (14%)
Previous MDS Therapy*		
Yes	27 (30%)	19 (23%)
No	62 (70%)	62 (77%)
IPSS Classification		
INT-1	28 (31%)	24 (30%)
INT-2	38 (43%)	36 (44%)
High Risk	23 (26%)	21 (26%)
FAB Classification		
RA	12 (13%)	12 (15%)
RARS	7 (8%)	4 (5%)
RAEB	47 (53%)	43 (53%)
RAEB-T	17 (19%)	14 (17%)
CMML	6 (7%)	8 (10%)
WHO Performance Status		
0	24 (27%)	28 (35%)
1	61 (69%)	48 (59%)
2	4 (4%)	4 (5%)
Missing	0	1 (1%)

Figure 2 Patient Disposition Between Treatment Arms



Reviewer's Table 2. Reasons for Patient Discontinuation from Study

Table 4 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	5 (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 (0145-5163 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.

For *Protocol Deviations, Treatment Compliance, Exposure to Decitabine or Supportive Care by Cycle, Statistical Considerations of Efficacy Variables, and Study Protocol Amendments* see original review filed on August 29, 2005.

6.1.4 Efficacy Findings

6.1.4.1 Co-Primary Efficacy Endpoint: Overall Response Rate (CR + PR)

The combined percentage of CR and PR according to the Verified Data Set was used to evaluate the Overall RR in the ITT and Evaluable Population analyses. To be classified as CR or PR using MDS IWG criteria, the patient was required to be RBC transfusion independent for 8 weeks during the time of response.

Summary of Changes in Outcomes following data verification is shown in Reviewer's Table 3 (Sponsor's Table 2 in Data Verification Report – Final).

The overall response rates in ITT and Evaluable Populations are unchanged after the data verification process. There were 2 patients in the DAC arm whose response assessments changed as a result of reassessment. One patient with hematological improvement (HI) was reassessed as having a CR. This patient had a bone marrow and cytogenetic CR response and became transfusion independent. The second patient originally classified as having a CR was reassessed as having an HI due to the presence of dysplasia in all bone marrow exams.

The number of patients with hematological improvement (HI), not a primary endpoint, increased by one in each treatment arm.

The median duration of response in all 15 patients increased from 266 days to 288 days. The median duration of HI or better in all 27 patients in the DAC arm increased from 253 days to 264 days, while it decreased from 212 to 191 days in the 6 patients with HI in the SC arm.

Reviewer's Table 3. Summary of Changes in Outcomes (ITT Population)

Various Patient Categories	Dacogen		Supportive Care	
Response	**Original**	**Revised**	**Original**	**Revised**
CR	8	8	0	0
PR	7	7	0	0
HI	11	12	5	6
Median Duration of Response (days)	266	288	NA	NA
Median Duration of Improvement (days)	253	264	212	191
% of patients RBC transfusion dependent at baseline who became independent on study	39%	23%	27%	15%
Change in Response (CR + PR) Response Duration Response Status	8 2		NA	
Change in Improvement (CR + PR + HI) Improvement Duration Improvement Status	16 1		1 1	

The revised analysis of Overall Response Rate following the data verification process is shown below in Reviewer's Tables 4 and 5 (data from Sponsor's Table 4).

Reviewer's Table 4. Overall Response Rate (CR + PR) in ITT Population

Best Hematological Response	Decitabine N=89	Supportive Care N=81	p-Value
Complete Response (CR)	8 (9%)	0	
Partial Reponse	7 (8%)	0	
Overall (CR + PR)	15 (17%)	0	< 0.001
Median time to CR + PR (days) (Range)	93 (55 – 272)	-	
Median duration of CR + PR (days)	288 (116 – 388)*	-	

*The range is based only on patients with confirmed disease progression dates.

Reviewer's Table 5. Overall Response Rate (CR + PR) in Evaluable Population

Best Hematological Response	Decitabine N=56	Supportive Care N=78
Complete Response (CR)	6 (11%)	0
Partial Reponse	6 (11%)	0
Overall (CR + PR)	12 (21%)	0
Median time to CR + PR (days) (Range)	91 (55 – 272)	-
Median duration of CR + PR (days)	288 (116 – 337)*	-

*See above.

In the ITT analysis, 8 patients had CR and 7 had PR for an Overall Response Rate of 17% (15/89). In the Evaluable Population analysis, 6 patients had CR and 6, PR for an ORR of 21% (12/56). The median time to response was 93 days, i.e. after about 2 cycles of therapy. The median duration of responses was 288 days. As noted above, the median time to response (93 days vs. 89 days) and the median duration of response (288 days vs. 270 days) were only slightly different in data verified results compared to the originally submitted results.

There were no responders in the SC arm. Hence, these findings were significant ($p < 0.001$ by two-sided Fisher's Exact Test).

Changes in the duration of response in ten patients as a result of data verification are shown in Reviewer's Table 6 (Sponsor's Table 3). Data on patients whose duration of response did not change as a result of data verification are not shown.

- Patient 1006-5045 originally classified as HI was reclassified as having a CR.
- Patient 1032-5067 originally classified as having a CR was re-assessed as having an HI.
- Two patients who were previously reported as having SD were determined to have HI (1 in DAC arm and 1 in SC arm).
- There were 2 patients (1 CR and 1 PR) whose duration of response increased and 6 patients (3 CR and 3 PR) whose duration of response decreased.

- Patients were censored at the time of study discontinuation if the date of disease progression was unknown.

These changes resulted in a small increase in the median duration of response, from 266 days to 288 days.

Reviewer's Table 6. Changes in Duration of Response Following Data Verification

Table 3 Changes in Duration of Response Following Data Verification

Patient	Best Response	Original Duration (days)	Revised Duration (days)	Overall Change (days)
0121-5065	CR	259	239	-20
0121-5081	CR	319	208	-111
1002-5148[a]	PR	189	>1[b]	-188
1003-5070	PR	239	302	+63
1006-5006	PR	131	116	-15
1007-5069	CR	346	388	+42
1008-5060	PR	342	>246[b]	-96
1033-5151	CR	294	>175[b]	-119
1006-5045[c]	CR	NA	>36[b, d]	+36
1032-5067[c]	HI	182	NA	NA

NA = not applicable
[a] Patient 1002-5148 had a bone marrow transplant 35 days after study discontinuation.
[b] Censored at the time of study discontinuation.
[c] Change in response status affected the change in response duration.
[d] No transfusion data found after date.

6.1.4.2 Response Rate in Patients with AML at Baseline

Nine patients in the DAC arm and three patients in the SC arm had AML at baseline as assessed retrospectively by the blinded independent hematopathology expert. Of these patients, 5/9 (56%) in the DAC arm and 0/3 in the SC arm had CR or PR. Among the patients with responses, there were 2 with CR, 1 with CRi (morphologic CR with incomplete blood count recovery), and 2 with PR. These limited data suggest that the patients re-classified as having AML at baseline responded very well to DAC therapy.

6.1.4.3 Co-Primary Efficacy Endpoint: Time to AML or Death

The results for this endpoint are unchanged from the original submission, and are shown in Reviewer's Table 7 below (data from sponsor's Table 6 in Clinical Summary - Revised). According to the co-primary endpoint model in the statistical analysis protocol, $p \leq 0.024$ was required to reach statistical significance. A median time to event was 121 days greater in the DAC group than in SC group. However, this difference had only a p=0.160 by two-sided log-rank test.

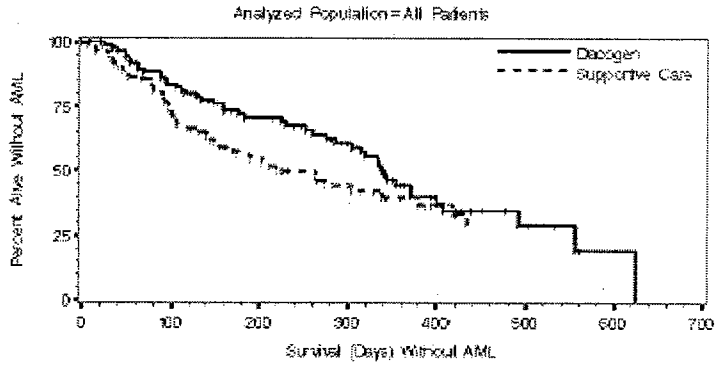
Reviewer's Table 7. Time to AML or Death* (ITT Population) at 92 Events

Parameter	Decitabine, N=89	Supportive Care, N=81	p-value
Number of events (%)	46 (52%)	46 (57%)	
Median time to event, days (95% CI)	340 (285 – 407)	219 (148 – 379)	0.160
Range, days (min – max)	24 - 624	7 - 432	

*Reflects analysis after 92 events. Patients who crossed over or never received randomized treatment are censored.

Sponsor's Figure 5 shows the Kaplan-Meier curves for this endpoint in the ITT population. There is an early separation between the curves, with the DAC curve showing delayed events. Subsequently, the DAC curve goes to zero because it reflects an actual event, while the supportive care group is truncated because the largest value is censored.

Figure 5 Time to AML or Death—All Patients



Reviewer's Figure 3

Subgroup analyses of Co-Primary Endpoints. Subgroup analyses of Overall Response Rate showed only one difference after data verification of results, one female patient with RA was classified as a responder and a male with RAEB-T, as a non-responder. Subgroup analyses of Time to AML or Death were unchanged in the results following data verification, and will not be recapitulated in this review.

6.1.4.4 Secondary Efficacy Endpoints

6.1.4.4.1 Overall Survival (unchanged from the original review)

In the ITT population, the median survival in the DAC arm was 391 days (range, 24-745) compared to 417 days (30-797) in the supportive care arm. The difference was not statistically significant.

6.1.4.4.2 Transfusion Requirements

In September of 2005, RBC and platelet transfusions were verified and entered in a new transfusion database. MDS IWG criteria were used to define transfusion dependence and independence, as described above. As a result of transfusion data verification and the application of the IWG criteria, the percentage of patients who were transfusion dependent and who became transfusion independent during the study changed, as shown above in Reviewer's Table 3. These percentages decreased in both arms – from 39% (35 patients) to 23% (20 patients) in the DAC arm and from 27% (22 patients) to 15% (12 patients) in the SC arm. The difference between the two arms remained, but it decreased from 12% to 8%.

- Responder Evaluation. At baseline, 10 of 15 responders were transfusion dependent. Nine were RBC transfusion dependent and 5 were platelet transfusion dependent. All became transfusion independent and remained independent during the response. In addition, the 6 patients who were independent at baseline remained transfusion independent during the response. These data are summarized in Reviewer's Table 8 (from Sponsor's Table 8 in Clinical Summary – Revised).

Reviewer's Table 8. Transfusion Status for DAC Responders (CR + PR)

RBC Transfusion Status	Platelet Transfusion Status
Dependent at Baseline, N=9 Dependent to Independent, N=9 (100%)	Dependent at Baseline, N=5 Dependent to Independent, N=5 (100%)
Independent at Baseline, N=6 Independent during Response, N=6 (100%)	Independent at Baseline, N=10 Independent during Response, N=10 (100%)

- HI Responder Evaluation (Reviewer's Table 9). At baseline 6 patients who were going to have an hematological improvement - erythropoietic (HI-E) response were RBC transfusion dependent. All 6 became transfusion independent during response. One patient was RBC transfusion independent baseline, became dependent during the study and then independent during response. One patient who was platelet transfusion dependent at baseline and six who were independent at baseline were all transfusion independent during the time of response (HI-P).

Reviewer's Table 9. Transfusion Status for HI-E and HI-P Responders

RBC Transfusion Status	Platelet Transfusion Status
Dependent at Baseline, N=6 Dependent to Independent, N=6 (100%)	Dependent at Baseline, N=1 Dependent to Independent, N=1 (100%)
Independent at Baseline, N=1 Independent during Response, N=1 (100%)	Independent at Baseline, N=6 Independent during Response, N=6 (100%)

Average number of transfusions per cycle did not decrease in the DAC arm, as shown in Reviewer's Table 10 (data from Sponsor's Table 9 in clinical Summary – Revised). They increased in both arms.

Reviewer's Table 10. Average Number of Transfusions per Cycle

Transfusion type	Period	All Decitabine N=89	Supportive Care N=81
RBC Transfusions Per Patient (mean)	Pre-Study (8 weeks)	2.5	1.5
	On-Study (6-week cycles)	2.8	1.8
Platelet Transfusions Per Patient (mean)	Pre-Study (8 weeks)	0.7	0.7
	On-Study (6-week cycles)	2.0	0.9

Responder analysis shows that transfusions decreased in DAC responders and increased in non-responders, as shown in Reviewer's Table 11 below (data from Sponsor's Table 9 in clinical Summary – Revised).

Reviewer's Table 11. Average Number of Transfusions per Cycle in DAC Responders and Non-Responders

Transfusion type	Period	DAC Responders N=15	DAC Non-Responders, N=74
RBC Transfusions Per Patient (mean)	Pre-Study (8 weeks)	1.6	2.7
	On-Study (6-week cycles)	0.8*	3.6
Platelet Transfusions Per Patient (mean)	Pre-Study (8 weeks)	1.0	0.6
	On-Study (6-week cycles)	0.7*	2.5

*Transfusions were 0 during CR or PR.

The frequencies of RBC transfusion over time are confounded by the decreases in the numbers of patients in each study arm during the study. Thus, by cycle 6 the number of patients in the

DAC arm decreased from 89 to 23 and in the Supportive Care arm, from 81 to 15. These data are shown in the August 30, 2005 review.

6.1.4.4.3 Improvement (CR + PR + Hematological Improvement).

In addition to the 17% CR + PR rate, there were 12 patients (13%) in the DAC arm with Hematological Improvement by IWG criteria (7 with HI-E Major, 7 with HI-P Major, and 3 with HI-N Major [patients could have more than one type of a major response]). Six patients in the Supportive Care arm had HI. The Overall Response Rate (CR + PR + HI) was 30% in the DAC arm and 7% in the Supportive Care arm. The difference between the two arms was statistically significant ($p < 0.001$). These data, as well as median days to response and median duration of response are shown in Reviewer's Table 12 (Sponsor's Table 7) below.

Reviewer's Table 12. Rate and Duration of Improvement (CR + PR + HI)

Table 7 Rate and Duration of Improvement (CR + PR + HI)

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%)	–
Hematologic Improvement (HI)	12 (13%)	6 (7%)	
Overall Response Rate (CR + PR + HI)	27 (30%)	6 (7%)	< 0.001[1]
Median Days to (CR + PR + HI) Response (Range)	41 (11–206)	89 (7–191)	–
Median Duration of (CR + PR + HI) Response (Range)	264 (50-449)[2]	191 (71–330)	–

1 From two-sided Fisher's Exact Test for equal Improvement (CR + PR + HI) Rate.

2 The range is based on patients with confirmed disease progression dates.

Source: *D-0007 Study Report: Table 14.2.1.1* Independent Reviewer's Assessments of Patients' Responses – All Patients; *Table 14.2.1.2* Independent Reviewer's Days to Initial Partial Response or Complete Response – All Patients; *Table 14.2.1.3* Independent Reviewer's Duration of Partial Response or Complete Response – All Patients; *Appendix 16.2.6.2* Listing of Duration of Best Response to Treatment – All Patients; *Appendix 16.1.9.4.2* Kaplan-Meier Estimates for Duration of Hematologic Improvement – All Patients

6.1.4.4.4 Quality of Life Analysis. See August 29, 2005 review.

6.1.4.4.5 Cytogenetic Responses. The only change from the August 29, 2005 review is the addition of Patient 0121-5002 in the DAC arm. This patient had a major cytogenetic response.

6.1.5 Clinical Microbiology. The Microbiology reviewer recommended approval of DAC. See July 15, 2005 review.

6.1.6 Efficacy Conclusions. (From August 29, 2005 review with changes as indicated by the results in the current submission).

1. The co-primary endpoints in the controlled Phase 3 trial were 1) Overall Response Rate (CR + PR) and 2) Time to Progression to AML or Death. The difference in Overall Response Rate (17%) in the DAC arm was significantly greater than in the supportive care arm (0%) ($p < 0.001$, Fisher's Exact test). The difference in Time to Progression to AML or Death between the DAC arm and the SC arm did not reach statistical significance ($p=0.160$ by log-rank test, $p=0.043$ by Wilcoxon test). Thus, efficacy of DAC was demonstrated by the Overall Response Rate, but not by Time to Progression to AML or Death.
2. Responses to DAC occurred in the controlled study and in the two single-arm studies at similar rates. Reviewer's Table 13 below shows the data for the ITT populations in the three studies. The mean ORR for the three studies was 22%.

Reviewer's Table 13. Summary of Overall Response Rates to DAC in MDS (ITT Populations)

Response	D-0007 N=89	PHC 97-19 N=98	PHC 95-11 N=66	Total, N=253
Overall (CR + PR)	15 (17%)	24 (24%)	17 (26%)	56 (22%)
CR	8 (9%)	19 (19%)	14 (21%)	41 (16%)
PR	7 (5%)	5 (5%)	3 (5%)	15 (6%)

3. The overall response rates in the Evaluable populations were higher than in the ITT populations, as shown in the Reviewer's Table 14 below. The ORR for the three studies was 31%. These higher response rates are to be expected, as patients who failed to complete at least two cycles of therapy, mostly because of early deaths, were excluded from the Evaluable populations. Two cycles of therapy appear to be the minimum length of treatment for a response. Patients adjudicated to have AML rather than MDS were also excluded from the Evaluable populations, but this exclusion did not influence the response statistics as AML patients responded at least as well as MDS patients to DAC therapy.

Reviewer's Table 14. Summary of Overall Response Rates to DAC in MDS (Evaluable Populations)

Response	D-0007 N=56	PHC 97-19 N=62	PHC 95-11 N=48	Total, N=166
Overall (CR + PR)	12 (21%)	23 (40%)	17 (35%)	52 (31%)
CR	6 (11%)	19 (33%)	14 (29%)	39 (23%)
PR	6 (11%)	4 (7%)	3 (6%)	13 (8%)

4. The clinical benefit of DAC-induced responses was normalization of blood counts and bone marrow blast percentages and elimination of the need for transfusions in patients who were

transfusion-dependent at baseline. Patients with responses who were pancytopenic but not transfusion-dependent at baseline had normalization of blood counts. Patients with responses who had elevated blast counts in the bone marrow at baseline had normalization of blast percentages.

5. The median time to response to DAC therapy was 93 days in the controlled trial. Responses were long lasting, as shown in Reviewer's Table 15 below. Median durations of response were 250 and 288 days in two studies and 146 days in one study, with very wide ranges in all studies.

Reviewer's Table 15. Duration of Response (ITT Populations)

Duration of Response (days)	D-0007	PCH 97-19	PCH 95-11
Median (range)	288 (116 – 388)	146 (1 – 545)	250 (78 – 456)
Mean ± SD	269.5 ± 23.7	148 ± 25	263 ± 21.3

6. Responses occurred in patients with each of the five FAB subtypes of MDS, as shown in Reviewer's Table 16 below. Small numbers of patients in some subtype categories do not permit comparison of response rates between FAB subtypes. Responses occurred at similar frequencies among IPSS Intermediate-1, Intermediate-2 and High Risk patients.

Reviewer's Table 16. Overall Response Rates (CR + PR) by IPSS and FAB Classifications (ITT Populations)

MDS subtype	D-0007 N=89	PCH 97-19 N=98	PCH 95-11 N=66	Total N=253
FAB Classification				
RA	2/12 (17%)	2/9 (22%)	1/7 (14%)	5/28 (18%)
RARS	0/7 (0%)	1/2 (50%)	-	1/9 (11%)
RAEB	9/47 (19%)	10/34 (29%)	8/26 (31%)	27/107 (25%)
RAEB-t	3/17 (18%)	5/33 (15%)	5/24 (21%)	13/74 (18%)
CMML	1/6 (17%)	4/14 (29%)	2/8 (25%)	7/28 (25%)
IPSS Classification*				
Low	0/0	4/6 (67%)	0/1	4/7 (57%)
INT-1	4/28 (14%)	4/18 (22%)	4/19 (21%)	12/65 (18%)
INT-2	7/38 (18%)	7/14 (50%)	6/25 (24%)	20/77 (26%)
High Risk	4/23 (17%)	9/37 (24%)	7/21 (33%)	20/81 (25%)
Total	89 (100%)	75 (77%)	66 (100%)	

*Not all patients in PCH 97-19 had cytogenetics and IPSS group could not be determined.

7. Responses occurred at about the same rate in all age groups, as shown in Reviewer's Table 17 below.

Reviewer's Table 17. Overall Response Rates (CR + PR) by Age (ITT Populations)

Age group	D-0007 N=89	PCH 97-19 N=98	PCH 95-11 N=66	Total N=253
Age in years, mean (range)	69 (31-85)	70 (51-87)	68 (37-84)	
<65	6/23 (26%)	4/22 (18%)	5/24 (21%)	15/69 (22%)
65-74	7/42 (17%)	11/48 (23%)	5/29 (17%)	23/119 (19%)
≥75	2/24 (8%)	9/28 (31%)	5/13 (38%)	16/65 (25%)

8. Response rates in females were higher in males in two of the studies and equal in one study (Reviewer's Table 18).

Reviewer's Table 18. Overall Response Rates (CR + PR) by Gender (ITT Populations)

Gender	D-0007, N=89	PCH 97-19, N=98	PCH 95-11, N=66	Total N=253
Male	8/59 (14%)	18/72 (25%)	7/46 (15%)	33/177 (19%)
Female	7/30 (23%)	6/26 (23%)	8/20 (40%)	21/76 (28%)

9. Analyses of response rates by race by race/ethnicity were not performed because most of the study subjects where White.

10. Response rates were higher in patients with no prior therapy for MDS than in patients with prior therapy, as shown in Reviewer's Table 19 below. *De novo* and secondary MDS patients had the same response rates.

Reviewer's Table 19. Overall Response Rates - Subgroup Analyses by Prior MDS Therapy and Type of MDS (ITT Populations)

	D-0007	PCH 97-19	PCH 95-11	Total
Prior MDS Therapy				
Yes	3/27 (11%)	1/11 (9%)	0/1	4/39 (10%)
No	12/62 (19%)	23/87 (27%)	17/65 (26%)	52/214 (24%)
Type of MDS				
De novo	13/77 (17%)	Not available	Not available	13/77 (17%)
Secondary	2/12 (16%)			2/12 (16%)

10. DAC treatment resulted in a statistically longer median Time to AML or Death than SC in IPSS High Risk patients (260 days vs. 79 days, unadjusted p=0.010 by two-sided log-rank test), but not in INT-1 and INT-2 patients.

11. DAC treatment had no effect on overall survival; median survival in the DAC treatment group was 391 days and in the supportive care group, 417 days. In PCH 97-19 study, median survival was 468 days, and in PCH 95-11 study, 401 days. Of note is that median survivals were similar in all three studies.

12. Rates of Hematological Improvement (CR + PR + HI) were greater and in the DAC treatment group (30%) than in the SC group (7%). This difference was statistically significant ($p < 0.001$). Median duration of improvement was 264 days in the DAC arm and 191 days in the SC arm.

    In PCH 97-19 study, the rate of Hematological Improvement (CR + PR + HI) was 41% (40/98 patients). In PCH 95-11 study, the rate of Hematological Improvement was 39% (25/66 patients).

13. In Quality of Life analysis, DAC patients had the following statistically superior parameters than SC patients: global health status, dyspnea and fatigue. In the supporting studies, performance status did not change during the course of DAC treatment.

14. Cytogenetic evaluation. In the DAC treatment arm, 9/48 (19%) of patients had a major cytogenetic response and 1/48 (2%) had a minor response. Among patients with CR + PR 53% (8/15) had a major cytogenetic response. In the SC arm 2 (6%) of patients had a major cytogenetic response. One had HI and one, progressive disease. There was a lack of correlation between IPSS Cytogenetic Prognostic Group and response to treatment with DAC.

15. The DAC dosage regimen is appropriate for this patient population, since in the controlled study DAC arm patients received 97% of their prescribed doses.

16. Temporary changes in treatment regimen occurred in 35% of patients, either delays of the next cycle (19%), delays of the next cycle and dose reduction (11%) or dose reductions (5%). Dose delays and dose reductions were due to adverse events.

Limitations of the available data:

1. The statistical plan of two co-primary endpoints (overall response rate and time to AML or death) with statistical significance p-values of ≤ 0.024 each was easily met by the ORR endpoint (p-value of < 0.001). Spontaneous responses in MDS are rare and did not occur in the SC arm of the controlled trial. DAC treatment did not result in statistically significant increased time to AML or death, a clinical benefit that may be difficult to document in MDS for a number of reasons (e.g. the very wide range of survival, the

advanced age of many patients who may die of other illnesses, the heterogeneity of MDS with varied probabilities of transformation to AML and of survival).

2. The criteria for responses in the controlled trial are the IWG response criteria for MDS, specifying not only the changes in the peripheral blood counts and the bone marrow but the duration of these changes. The earlier response criteria in the Phase 2 trials differ primarily by the absence of the minimum duration of the hematopoietic changes.
3. The sponsor comments that the rate and durability of response, conversion to a better response, time to AML or death, and survival could have been negatively impacted by the design of the randomized trial. (Patients who achieved a CR, or a PR or an HI by Cycle 4 were to receive only two additional cycles of therapy and then be removed from the study.)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

As described in the August 29, 2005 review, a total of 240 patients with MDS had received DAC in the three primary studies (154 patients in PCH 95-11 and PCH 97-19, and 83 randomized plus 3 crossover patients in the randomized trial D-0007). The dose of DAC was the same in all 3 studies (15 mg/m^2 IV every 8 hours for 3 consecutive days). The 4-hour infusion (in two 2-hour aliquots) in the Phase 2 studies and the 3-hour infusion in the D-0007 trial did not appear to cause any difference in effectiveness or adverse symptomatology. Data from these studies cannot be fully integrated. The Phase 2 studies used WHO adverse event grading criteria, the D-0007 trial used NCI CTC. In addition to these three studies, the sponsor submitted older Phase 1/2 studies in 129 patients with MDS or AML, in which higher dosing regimens were administered. These studies cannot be pooled because of differences in reporting formats, but the data indicate primary toxicity to be dose-dependent myelosuppression.

The 120-Day clinical Safety Update submitted to the FDA on March 1, 2005 contained safety data from the time of NDA submission on October 29, 2004 to January 31, 2005. The present submission (Approvable Letter Safety Update) includes data obtained from February 1, 2005 to September 30, 2005.

The present Safety Update contains no additional information regarding the completed D-0007 trial, but contains some information from all ongoing sponsor trials under IND 71,160, including DAC-011, DACO-017, DACO-018, DACO-020, and DACO-021. All SAEs received during the reporting period are included in this Safety Update.

There are no new conclusions regarding the safety profile of DAC as a result of the safety information in this submission.

7.1.1 Deaths

Eighteen patients died while on study during this period, 1 in DACO-017, 3 in DACO-018, 6 in EORTC D-2108, 7 in EORTC 06011, and 1 in PHI/082. Fourteen patients had received DAC prior to death, 4 received Supportive Care.

Seven deaths were considered as definitely, probably or possibly related to DAC therapy. The SAEs resulting in deaths were:

- One case of febrile neutropenia, pneumonia, and cerebral ischemia,
- Four cases of sepsis accompanied by refractory hypotension, or cardiac arrest, or pneumonia,
- One case of renal failure, and
- One case of aspergillus pneumonia.

7.1.2 Other Serious Adverse Events

Numbers in parentheses state the numbers of patients in the study.

- In DAC-011 (N=15): 2 cases of febrile neutropenia, 2, of thrombocytopenia, 2 of sepsis, 1 each of chest pain, bacteremia, cellulitis, and cerebral hemorrhage.

- In DACO-017 (N=15): 7 cases of febrile neutropenia, 2 of pneumonia, 1 each of diarrhea, catheter site infection, bacteremia, UTI, and elevated blood creatinine.

- In DACO-018 (N=16): 4 cases of febrile neutropenia, 2 each of pneumonia and of chills, 1 each of neutropenia, cellulitis, fungal infection, sepsis, cerebral ischemia, and sensory neuropathy.

- In DACO-020 (N=8): 1 case of febrile neutropenia.

- In EORTC D-2106 (06011) (N=132): 3 cases each of febrile neutropenia, sepsis and pneumonia, 2 cases of neutropenia, and 1 each of cardiac arrest, diarrhea, pyrexia, bronchial infection, neutropenic infection, septic shock, sinusitis, tooth abscess, and phlebitis.

- In EORTC D-2108 (00331) (N=56): 2 cases each of febrile neutropenia and pyrexia, 1 case each of neutropenia, abdominal pain, diarrhea, gingival edema, vomiting, aplasia, anaphylactic reaction, pneumonia, aspergillus pneumonia, sinusitis, laryngeal edema, and stridor.

- In PH1/082 (N=33): 1 case of neutropenic infection.

- In PH1/094 (N=9): 1 case of neutropenic sepsis.

- In Protocol [redacted] (N=14): 5 cases of neutropenia.
- In Protocol [redacted] (N=6): 1 case each of febrile neutropenia, hematemesis, and vomiting.

7.1.3 Other Significant Adverse Events

Four serious and unexpected treatment-related AE cases were reported during this period. These were 1) one case of anaphylaxis (swelling of gingival, stridor and swelling of larynx/trachea), 2) two cases of elevation of troponin I (probably related to depsipeptide rather than to DAC), and 3) one case of apical lusters on X-ray, which turned out to be due a tooth abscess, not an unexpected event.

7.1.4 Other Search Strategies.

A literature search in PubMed revealed no new publications on the safety of DAC.

7.1.5 Common Adverse Events

The most common adverse events in DAC-011 study (N=15) were neutropenia, thrombocytopenia, anemia, febrile neutropenia, diarrhea, nausea, asthenia, bacteremia and hypoalbuminemia.

In Protocol ID [redacted] study (N=100) the most common adverse events were fatigue, nausea, dyspnea, hyperbilirubinemia, hypoalbiminemia, limb edema, elevated ALT/AST, cough, and vomiting.

These findings are consistent with those previously reported in the original submission and the 120-day safety update.

7.1.6 Less Common Adverse Events. Described above in 7.1.3.

7.1.7 Laboratory Findings. Described under adverse events. There are no new findings in the Safety Update.

7.1.8 Vital Signs. See August 29, 2005 review.

7.1.9 Electrocardiograms (ECGs). See August 29, 2005 review.

7.1.10 Immunogenicity. See August 29, 2005 review.

7.1.11 Human Carcinogenicity. See August 29, 2005 review.

7.1.12 Special Safety Studies. See August 29, 2005 review.

7.1.13 Withdrawal Phenomena and/or Abuse Potential. N/A.

7.1.14 Human Reproduction and Pregnancy Data. Exposure in pregnant women has not been reported.

7.1.15 Assessment of Effect on Growth. Effects on growth have not been reported in human subjects.

7.1.16 Overdose Experience. Early experience with DAC used 5- to 10-fold higher doses. There have been no overdoses in the MDS trials.

7.1.17 Postmarketing Experience. DAC has not been marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See August 29, 2005 review. The Safety Update reports that a total of 150 patients were enrolled in studies DAC-011, DACO-017, DACO-018, DACO-020, DACO-021 and Protocol ID [redacted] at the time of this report. A total of 144 patients have completed at least one cycle of therapy and, combined, have received a total of 708 patient cycles.

Most of the patients (98) had MDS (ID [redacted] , DACO-18, DACO-020 and DACO-021); 33 had AML (DAC-011, DACO-017, DACO-018 and DACO-021). There were 97 males and 48 females (gender unknown in 5), ages ranged from 39 to 90 years (median ages of 65 to 72 years).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See review of August 29, 2005.

7.2.3 Adequacy of Overall Clinical Experience

(From August 29, 2005 review).

- Three studies were submitted in this NDA, one controlled by best supportive care arm, the other two single-arm studies. In all, 240 patients were exposed to DAC in these studies. In addition, a multi-center Phase 1/2 study enrolled 38 patients, who received higher doses of DAC than the MDS patients. An EORTC trial of 220 patients randomized to DAC or placebo is underway. Altogether, this number of patients should provide adequate safety data.
- There are adequate numbers of male and female patients (in about 2:1 ratio, which is characteristic for MDS).
- There is limited racial or ethnic representation, as most of the study subjects were White (Caucasian).

- Doses and durations of DAC in the three studies submitted in this NDA are the same as proposed in the submitted package insert.
- One best supportive care-controlled randomized study of adequate size supported by two single-arm studies with similar results is sufficient to answer critical questions.
- There is only one approved drug in this drug class, the ribonucleotide analog, azacitidine. The toxicity profiles of the two drugs are very similar, if not identical. Both drugs act on replicating cells, inhibit DNA methylation at CpG islands, induce cell differentiation and result in cell cytotoxicity. They have no P450 isozyme interaction, are mainly excreted in bile, but show little hepatotoxicity except in hepatically impaired patients, and little evidence of renal toxicity in absence of cardiac failure and dehydration.
- The following exclusionary criteria that were used in the trials also are valid for the use of DAC in practice as the drug may pose additional dangers: autoimmune anemia, thrombocytopenia, active infection, neutropenia, HIV, uncontrolled cardiac disease, mental illness or other conditions preventing full cooperation.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See August 29, 2005 review.

7.2.5 Adequacy of Routine Clinical Testing

See August 29, 2005 review.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See August 29, 2005 review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

See August 29, 2005 review.

7.2.8 Assessment of Quality and Completeness of Data

See August 29, 2005 review.

7.2.9 Additional Submissions, Including Safety Update

See above in 7.1.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

(From August 29, 2005 review)

- Virtually all patients treated with DAC reported adverse events, more than patients in the control arm.
- Most common adverse events were hematologic, especially thrombocytopenia, febrile neutropenia, leukopenia, and anemia.
- Likewise common were gastrointestinal disorders, such as nausea, vomiting, constipation, diarrhea, abdominal pain, stomatitis, dyspepsia and ascites.
- Infections were common, probably related to leukopenia, and included pneumonia, catheter infections, skin infections, and fungal infections.
- Fever, lethargy, peripheral edema, a variety of pains, headaches, hypesthesias, dizziness, insomnia, and confusion occurred more commonly in the DAC group than in the control group.
- Ecchymoses, patechiae, pallor, rashes, erythemas and other skin disorders were more common in the DAC group than in the control group.
- Hepatic enzyme elevations and renal function abnormalities were rare and their relationship to DAC uncertain.
- There were no drug-related deaths. (Note: see 7.1.1 above)
- SAEs were related to the MDS and mechanism of action of the drug resulting in neutropenia and infection, anemia and cardiovascular complications, thrombocytopenia and hemorrhage.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The adverse events tables for controlled study D-0007 and the Phase II studies cannot be fully integrated for reasons stated in 7.1. The incidence of many adverse events appear to be similar, but hematological adverse events are unexplainably less frequent in the Phase II studies.

7.4.2 Explorations for Predictive Factors

See August 29, 2005 review.

7.4.3 Causality Determination

Since the pathophysiology of MDS results in similar adverse events as DAC, the sponsor chose to use a numerical difference between DAC-treated patients and supportive care patients experiencing a particular event to determine causality.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

(From August 29, 2005 review).

The dosing schedule used in the three studies described in this NDA, which resulted in similar efficacy and safety, lends confidence to this dosage regimen. In the controlled study, DAC arm patients received 97% of prescribed doses.

- Thus, the starting dose of 15 mg/m^2 infused i.v. over 3 hours every 8 hours for three days every six weeks is an appropriate starting dose.
- Dose modifications depended on adverse events or lack of efficacy.
- There were no dose modifications for patients with hepatic or renal impairment, as these patients were excluded from the studies.
- Effect of food was not specifically investigated, since the drug is administered i.v.

The regimen can be improved in the following areas:

- DAC would be easier to administered if it could be administered subcutaneously rather than intravenously, or intravenously once daily over a shorter infusion period. These studies are being carried out either by the sponsor or by academic investigators. The most promising regimen appears to be 20 mg/m^2 infused i.v. over 1 hour once daily for 5 days every 4 weeks. This regimen appears to be at least as effective and safe as the above regimen; however, only relatively few patients been so treated, making this conclusion premature.

Appropriate dose modifications should be explored for patients with mild to moderate hepatic or renal impairment.

8.2 Drug-Drug Interactions

The use of concomitant medications paralleled the pattern of adverse events observed. For that reason, concomitant medications were used far more frequently in the DAC group. Possible potentiation by tamoxifen in causing severe thrombocytopenia (40,000/mm^3) with subsequent intracerebral bleeding occurred in one case.

8.3 Special Populations

Race. As noted above, the few non-White patients (4% African Americans, 2% from other origins) precluded analysis by race. About 93% of patients were White in the D-0007 trial. In the Phase II trials from Netherlands, Belgium and Germany most patients were presumed White, but racial background was not always entered in CRFs.

Gender. Data are fully presented in the August 29, 2005 review. In summary, in the randomized D-0007 trial

- Males in the DAC arm reported the following adverse events more frequently than females : neutropenia, thrombocytopenia, anemia, abdominal pain, fever, asthenia,

hyperbilirubinemia, pneumonia, cellulitis, staphylococcal infections, hyponatremia, erythema, splenomegaly, dyspnea, and sweating.

- Females in the DAC arm reported the following adverse events more frequently than males: febrile neutropenia, nausea, constipation, loose stools, stomatitis, headache, crackles in the lung, ecchymosis, pruritis and patechiae.
- Males in the SC arm reported the following adverse events more frequently than females: febrile neutropenia, splenomegaly, cardiac disorders, constipation, fever, pneumonia, cellulites, nervous system and psychiatric disorders, cough, dyspnea, ecchymosis, erythema, hyperhidrosis, and patechiae.
- Females in the SC arm had the fewest adverse events. The only adverse event in which they surpassed males was headache.

Even though the numbers of events were probably too small to draw conclusions, at least a doubling of patients with adverse events (male vs. female) in a background where these adverse events are low in the SC arm suggest the following as possibly reflecting significant differences between genders:

- In males, splenomegaly, abdominal pain, hyperbilirubinemia, pneumonia, and erythema.
- In females, febrile neutropenia, and stomatitis.

8.4 Pediatrics. MDS is rarely seen in the pediatric age group.

8.5 Advisory Committee Meeting. There are no plans present this application to the Oncology Drugs Advisory Committee.

8.6 Literature Review. See August 29, 2005 review.

8.7 Postmarketing Risk Management Plan

There is an on-going EORTC trial in which MDS patients have been randomized to DAC or SC, and the primary endpoint is overall survival.

8.8 Other Relevant Materials. None.

9 OVERALL ASSESSMENT

9.1 Conclusions

1. DAC is an agent that reduces hypermethylation of DNA, which is common in MDS. Decreased hypermethylation (or hypomethylation) of DNA is thought to result in restoration of normal growth control in hematopoietic cells. As a result, a response to DAC results in complete or partial normalization of blood counts and bone marrow blast percentages (where previously abnormal), and patients are no longer dependent on transfusion of RBCs and/or platelets. Elimination of transfusion dependence results in decreased discomforts and decreased risks of transfusion hemosiderosis, transfusion

reactions, and possible infections. DAC treatment has not been shown to decrease the risk of development of AML or to increase overall survival.

2. The data in this submission demonstrate that a minority of MDS patients (about 17%-26% in the ITT populations of the three studies) had long-lasting complete or partial responses to DAC. In the controlled trial, 17% of patients in the DAC treatment arm had a response, while none of the patients in the supportive care arm had a response. This difference in response rates between the two arms was highly significant ($p < 0.001$).
3. The response rates were higher in those patients who were able to complete at least two cycles of therapy, the minimum required for a response. Among these patients, the response rates were about 21% to 40% in the three studies (the wide range in response rates between studies may have been due in part to differences in definitions of responses).
4. The responses were long-lasting. Median ranges for the three studies were 146, 250, and 288 days in the three studies.
5. Thus, DAC is useful for eliminating transfusion dependence in patients with complete and partial responses and also in Hematological Improvement patients (whose responses failed to meet the criteria for partial response). About 28% to 41% of DAC-treated patients lost the need for transfusions.
6. Subgroup analyses showed that responses to DAC occurred at similar frequencies in all FAB classification subtypes, in High-Risk, INT-2 and INT-1 IPSS subtypes, in all age ranges, in both genders, in patients with prior therapy for MDS and in patients without prior therapy, and in *de novo* MDS and secondary MDS. IPSS prognostic group did not predict the probability of response.
7. Major and minor cytogenetic responses occurred in about one-half of complete and partial responders.
8. Quality of life analyses showed improved global health status, dyspnea and fatigue in the DAC treated patient group but not in supportive care patient group.

9.2 Recommendation on Regulatory Action

1. The data presented in this NDA support the approval of DAC for treatment of MDS patients with all FAB subtypes and High-risk, INT-2, and INT-1 IPSS subtypes, previously treated as well as untreated patients, and patients with *de novo* or secondary MDS.

2. DAC is an inhibitor of DNA methylation, promoting differentiation of hematopoietic cells, and is also a cytotoxic agent causing cell cycle arrest and apoptosis. It is effective in about 17% to 26% of MDS patients in completely or partially restoring normal blood cell counts and normal percentage of blasts in the bone marrow, and in reducing or eliminating transfusion dependence. The therapeutic effects are generally long lasting. DAC treatment has not been shown to result in survival benefit. The goals of decitabine treatment should be to restore normal blood cell counts and bone marrow blast percentages and to eliminate transfusion dependence.

3. The dose of decitabine is 15 mg/m^2 administered intravenously over 3 hours; this dose is repeated every 8 hours for 3 days every six weeks. The dose is adjusted according to blood cell counts. Patients should be treated for a minimum of four 6-week cycles.

4. Reviewer's recommendations for decitabine (Dacogen™) labeling are incorporated into this review.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Postmarketing safety reports (21 CFR 314.80).

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

- As noted above, a controlled trial, in which MDS patients are randomized to DAC or placebo with overall survival as the primary endpoint, is on-going under EORTC auspices.
- Studies of metabolism of decitabine, in particular whether any of the cytochrome P450 enzymes is involved in the biotransformation of decitabine,
- Studies of pharmacokinetics and safety of decitabine in patients with mild hepatic impairment,
- Studies of pharmacokinetics and safety of decitabine in patients with mild to moderate renal impairment, and
- Studies of dosing regimens that are at least as effective as the present one, and can be administered without a three day hospitalization.

9.4 Labeling Review

Sponsor's proposed labeling was extensively changed. See section 10.1.

The trade name was reviewed by Division of Medication Errors and Technical Support (DMETS); there are no issues with the proposed name.

A medication guide is not necessary, as DAC will be administered by health care professionals.

18 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

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4/3/2006 05:38:00 PM
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Rajeshwari Sridhara
4/5/2006 12:22:41 PM
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Aloka Chakravarty
4/5/2006 01:52:43 PM
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Deputy Office Director Memo

Re:	NDA Submission Number 21-790
Sponsor:	SuperGen Pharmaceuticals
Product:	Decitabine, Dacogen™
Submission Date:	November 1, 2004
PDUFA Action Date:	September 1, 2005

Brief summary and recommended action

SuperGen Pharmaceuticals seeks market approval for decatibine (Dacogen™), a nucleoside analogue, for the treatment of patients with Myelodysplastic Syndrome (MDS). The reviews from each discipline are complete. I concur with the recommendation for an Approvable Action based on deficiencies identified during inspection of the two largest enrolling centers that participated in the major efficacy trial, as described below. The CMC, Pharm/Tox, Microbiology, and Biopharm reviews have not uncovered major deficiencies.

Clinical/Statistical/Scientific Integrity issues: The efficacy data are derived from a single randomized, controlled phase 3 trial of Dacogen™ vs (best) supportive care in 170 patients with histological MDS of all subtypes and two phase 2 non-controlled trials in similar patient populations, with sample sizes of 66 and 98 subjects. In the phase 3 trial, referred to as D-0007, the Dacogen™ arm received dacatibine at 15 mg/m^2 injection as nine 3-hour infusions over 3 days (one infusion every 8 hours for 3 days) per 6-week cycle administered in the hospital, clinic, or through home infusion care. The dose and schedule were selected based on phase 1 and phase 2 studies in MDS and other disease populations.

D-0007 was designed with the co-primary efficacy endpoints: (a) proportion of responders (CRs + PRs) and (b) time to progression to Acute Myeloid Leukemia (AML) or death. The phase 2 supportive studies were primarily designed to assess response rate. Definitions for response in trial D-0007:

CR is defined as follows:
Bone marrow: Repeat bone marrow showing >5% myeloblasts with normal maturation of all cell lines, with no evidence for dysplasia.
Peripheral blood (values must last at least 2 months): Hgb > 11g/dL, ANC ≥ 1500/mm^3, platelets ≥ 100,000/mm^3 (patient not receiving erythropoietin, myeloid growth factor, or thrombopoietic agent), absence of blasts, absence of dysplasia.

PR is defined as follows:
Bone marrow: Blasts decreased by 50% or more over pretreatment, or a less advanced MDS FAB classification than pretreatment, normal maturation of all cell lines, without evidence of dysplasia.
Peripheral blood: As in CR.

Of note, in order to be classified as a CR or PR, the patient must have been transfusion independent for a minimum of 8 weeks in absence of administration of growth factors during the period of response.

As per Dr. Kaminsky's medical officer review, noteworthy findings from the phase 3 trial include a significant difference in the ITT population between dacatibine-treated patients and controls in overall response rate:

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)	–

The findings from the more clinically meaningful endpoint of time to progression to AML or death were not significant at $p < 0.025$ (pre-specified level of significance for co-primary endpoints) See table below.

I.T.T. population – time to progression to AML or death

Parameter	Decatibine, N=89	Supportive care N=81	p-value
Number of events (%)	46 (52%)	46 (57%)	
Median time to event, days (95% CI)	340 (285-407)	219 (148-379)	0.043, 0.160*
Range, days (min – max)	24 – 624	7 – 432	

*p=0.0043 two-sided Wilcoxon test for homogeneity of survival distributions, p=0.160 two-sided log-rank test.

However, because the endpoint of response rate includes transfusion independence, even the finding of a significant difference in this outcome measure alone is a demonstration of clinical benefit in its own right and could therefore support a full approval. Thus, verification of transfusion requirements and transfusion independence is critical to ensuring the intergrity of these outcome measurements. A bioresearch monitoring inspection was carried out by the Division of Scientific Investigation at the two largest enrolling sites in the phase 3 trial. The finding that transfusion data could not be verified in a high proportion of the records evaluated (approximately 50%, or 6/12 records at one site and 3/11 records at the second site) as well as other protocol violations and deviations; see the consult from DSI) led to the conclusion that data collected by these two sites are unreliable. The approvable letter contains the request to either confirm transfusion requirements in study D-0007 or submit results of response rates and transfusion requirements from an ongoing, EORTC sponsored, randomized, controlled trial of Dacogen™ when such data are available.

The phase 2 trials enrolled a patient population and used a dosing regimen similar to that in D-0007. The primary outcome measure for both trials was best hematologic response. Response rates were similar for both trials; approximately 25%. Because the definition of response differed from the phase 3 trial and there was no internal control, these data

can provide supportive evidence for drug effect but cannot be used to draw firm conclusions about efficacy or safety.

In the controlled trial, D-0007, hematologic and gastro-intestinal toxicities were the main category of adverse events that were observed at higher rates relative to the controls. As per Dr. Justice's division director memo, I concur that the adverse event profile is acceptable in relation to the clinical benefit of eliminating or reducing transfusion dependence. This further underscores the need for data verification to confirm clinical benefit.

In summary, I concur with the review division's recommendation to issue an approvable letter for this application. Approval will require submission of an amended application addressing the clinical deficiencies described above.

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/s/

Karen Weiss
8/30/2005 05:29:41 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-790
Submission Code	0000, BM, SU
Letter Date	October 29, 2004; February 14, 2005; February 28, 2005
Stamp Date	November 1, 2004
PDUFA Goal Date	September 1, 2005
Reviewer Name	Edvardas Kaminskas, M.D.
Review Completion Date	August 29, 2005
Established Name	Decitabine
(Proposed) Trade Name	Dacogen™
Therapeutic Class	Antineoplastic
Applicant	SuperGen, Inc.
Priority Designation	S
Formulation	Lyophilized powder
Dosing Regimen	Intravenous
Indication	Myelodysplastic syndrome
Intended Population	Adults

Table of Contents

The List of Abbreviations and Definitions of Terms on the following pages are from the sponsor's NDA submission. Not all are used in the review.

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
95% CI	95% confidence interval
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase (see also SGPT)
AML	acute myeloid leukemia
ANC	absolute neutrophil count
Ara-C	cytosine arabinoside
AST	aspartate aminotransferase (see also SGOT)
b.i.d	twice daily
BM	bone marrow
BN rats	Brown Norway rats
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
Bx	biopsy
cAMP	cyclic adenosine monophosphate
CBC	complete blood count
CFR	Code of Federal Regulations
cGCP	current Good Clinical Practices (as defined in CFR and ICH Guidelines)
cGMP	current Good Manufacturing Practices
CI	confidence interval
cm	centimeter
CMML	chronic myelomonocytic leukemia
COPD	chronic obstructive pulmonary disease
CR	complete response
CRA	Clinical Research Associate
CRF	case report form
CT	computerized tomography
CTC	common toxicity criteria
CVA	cerebrovascular accident
DAC	Dacogen, decitabine (5-aza-2'-deoxycytidine)
dL	deciliter
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Agency
EORTC	European Organization for Research & Treatment of Cancer
EOP2	End of Phase II (meeting with FDA)
EPO	erythropoietin
FAB	French-American-British Co-operative Study Group classification system
FDA	Food and Drug Administration
γ-GT	gamma-glutamyl-transpeptidase

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (Cont'd.)

Abbreviation	Definition
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
h	hour(s)
Hct	hematocrit
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HI	hematologic improvement
HI-E	hematologic improvement, erythroid
HI-N	hematologic improvement, neutrophils
HI-P	hematologic improvement, platelets
HIV	human immunodeficiency virus
HLGT	MedDRA high level group term
HLT	MedDRA highest level term
HMBA	hexamethylenebisacetamide
HPLC	high-performance liquid chromatography
IC	Informed Consent
ICH	International Conference on Harmonization
IDSR	Investigational Drug Shipping Request
IEC	Independent Ethics Committee
IND	Investigational New Drug application
IPSS	International Prognostic Scoring System
IQR	Interquartile range
IRB	Institutional Review Board
ISCN	International System for Human Cytogenetic Nomenclature
ITT	intention-to-treat (patient population)
IVRS	Interactive Voice Response System
IWG	International Working Group
i.v.	intravenous(ly)
L	liter
LDH	lactate dehydrogenase
MAC	Mycobacterium avium complex
m	minute
M	molar (mole/L)
m^2	square meters
MDS	myelodysplastic syndromes
MedDRA	medical dictionary for regulatory activities
min	minimum
mL	milliliter
NA	not applicable
NCI	National Cancer Institute (US)

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (Cont'd.)

Abbreviation	Definition
ND	not done
NE	not evaluable
nm	nanometer
nM	nanoMolar
PAC	Port-a-Cath
PD	progressive disease
PI	principal investigator
PK	pharmacokinetics
Plt. ct.	platelet count
p.o.	by mouth (per os)
PR	partial response
PRBC	packed red blood cells
PT	MedDRA preferred term
QLQ	quality of life questionnaire
QC	quality control
RA	refractory anemia
RAEB	refractory anemia with excess blasts
RAEB-t	refractory anemia with excess blasts in transformation
RAF	Return Authorization Form
RARS	refractory anemia with ringed sideroblasts
RBC	red blood cell
RPD	rapidly progressive disease
SAE	serious adverse event
SD	stable disease
±SD	±standard deviation
SGOT	serum glutamic-oxaloacetic transaminase (see also AST)
SGPT	serum glutamic-pyruvic transaminase (also ALT)
SOC	MedDRA system organ class
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life (of drug)
TIA	transient ischemic attack
TBP	Therapeutic Products Directorate (Canada)
USP	United States Pharmacopeia
UA	urinalysis
UE	unevaluable
ULN	upper limit of normal range (laboratory)
WBC	white blood cells
WIC	written informed consent
WHO	World Health Organization
µL	microliter
µM	microMolar

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

1. Approval of decitabine for treatment of patients with myelodysplastic syndrome (MDS). **The data in this NDA were reviewed as submitted. As described below, these data suggest that decitabine is approvable for the stated indication. However, inspections of the two largest sites of subject enrollment by the Division of Scientific Investigations led to the conclusion that data collected by these two sites are unreliable (see below in 4.3 Data Quality and Integrity). Therefore, from a clinical perspective, approval of decitabine is contingent on the submission by the sponsor of verifiable data supporting the efficacy and safety of decitabine in MDS.**

2. Decitabine is an inhibitor of DNA methylation, promoting differentiation of hematopoietic cells, and is also a cytotoxic agent causing cell cycle arrest and apoptosis. It is effective in about 17% to 26% of MDS patients in completely or partially restoring normal blood cell counts and normal percentage of blasts in the bone marrow, and in reducing or eliminating transfusion dependence. The therapeutic effects are generally long lasting (median durations of response were 146 to 266 days). Decitabine treatment has not been shown to result in survival benefit. Responses to decitabine have been shown to occur in patients with all FAB subtypes, with High-risk, INT-2, and INT-1 IPSS subtypes, in previously treated as well as untreated patients, and in patients with *de novo* or secondary MDS.

3. The dose of decitabine is 15 mg/m^2 administered intravenously over 3 hours; this dose is repeated every 8 hours for 3 days every six weeks. The dose is adjusted according to blood cell counts. Patients should be treated for a minimum of four 6-week cycles. A complete or partial response may take longer than 4 cycles. Treatment may be continued for as long as the patient continues to benefit.

4. Reviewer's recommendations for decitabine (Dacogen™) labeling are not incorporated into this review for reasons stated above.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Standard procedures for adverse event reporting.

1.2.2 Required Phase 4 Commitments

Completion of EORTC 06011 Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.

1.2.3 Other Phase 4 Requests

The sponsor should evaluate in the post-marketing phase

- Metabolism of decitabine, in particular whether any of the cytochrome P450 enzymes is involved in the biotransformation of decitabine,
- Pharmacokinetics and safety of decitabine in patients with mild hepatic impairment, and
- Pharmacokinetics and safety of decitabine in patients with mild to moderate renal impairment.
- Dosing regimens that are at least as effective as the present one, and can be administered without a three day hospitalization.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Product name, class, starting dose and route of administration: Dacogen™ for Injection contains decitabine, an analogue of the natural deoxyribonucleoside 2'-deoxycytidine. Decitabine promotes cell differentiation and is also cytotoxic. Dacogen is administered by a 3-hour intravenous infusion at a starting dose of 15 mg/m^2 every 8 hours for three days every 6 weeks.
Indications and populations studied: Adult patients with all FAB subtypes of myelodysplastic syndrome.
Number of pivotal efficacy and safety trials: One Phase III controlled trial, supported by two single-arm Phase II trials.
Number of patients enrolled in the primary trials: 170 in the Phase III trial and 164 in the Phase II trials.
Overall number of patients in the safety database and extent of exposure: 240 patients in the three primary studies and 183 patients in six ongoing studies. In the Phase III controlled trial, the average dose per treatment cycle was 247 mg, median number of cycles was 4, and the median cumulative dose received was 735 mg (range, 203-2614 mg).

1.3.2 Efficacy

Efficacy of decitabine in treatment of MDS is demonstrated in the controlled, randomized Phase III trial D-0007, in which of 89 patients randomized to decitabine 83 were treated with decitabine (plus 3 crossover patients from the supportive care arm) and 81 patients received supportive care only. Similar efficacy results were found in the two single arm, multicenter Phase II studies, PCH 95-11 and PCH 97-19, in which 66 patients and 98 patients, respectively, were treated with decitabine. All three trials had enrolled patients with MDS of all FAB subtypes and of high-risk, intermediate-2 and intermediate-1 IPSS categories.

Endpoints: There were two primary endpoints in the controlled trial, overall response rate (complete or partial) and time to progression to acute myeloid leukemia or death. Secondary endpoints included survival, transfusion requirements, overall response rate plus the rate of hematological improvement (a lesser than partial response), quality of life measures, and cytogenetic response. The primary endpoints in both Phase II studies were best hematological response (defined as complete remission, partial remission, improvement, stable disease, relapse, or progression), transfusion requirements, and changes in performance status.

Endpoint issues:

- The sponsor initially proposed overall response rate as the primary endpoint for the controlled trial, while the Agency suggested time to progression to AML or death. Both became co-primary endpoints. The possibility of achieving a statistically significant delay in time to progression to AML or death with decitabine treatment was suggested by the CALGB 9221 trial in which MDS patients were treated with azacitidine, an agent with a similar mechanism of action. A later statistical analysis of this trial by the Agency concluded that such a delay was not demonstrated. Thus, there is so far no evidence that any agent is effective in prolonging the time to progression to AML or death in MDS patients.

- The definitions of overall response rates differ between the pivotal controlled trial and the Phase II studies, as criteria for response rates changed with publications by international working groups. The main difference is that a complete or partial response by the later criteria needs to be maintained for at least 8 weeks, while the earlier criteria have no such requirement.

Efficacy Conclusions:
(Please see Executive Summary 1.1. The conclusions below were based on data as submitted).

- Patients treated with decitabine had an overall response rate of about 17% (in ITT population) as compared to no responses in the supportive care patients. This difference was statistically significant ($p < 0.001$). Decitabine-treated patients in the single-arm studies had overall response rates of 24% and 26% (ITT populations).
- Time to progression to AML or death was not significantly different in decitabine-treated patients from that in supportive care patients ($p=0.160$).
- The clinical benefit of decitabine-induced responses was normalization of blood counts and bone marrow blast percentages and elimination of the need for transfusions in patients who were transfusion-dependent at baseline.
- The responses were long-lasting. The median durations of responses were 266 days, 146 days, and 250 days in the controlled trial D-0007, PCH 97-19 study, and PCH 95-11 study, respectively. The median time to response in the controlled trial was 89 days.
- Subgroup analyses revealed:
    - Patients with MDS of all FAB subtypes and IPSS classifications had approximately similar response rates.
    - Patients of all age ranges had similar response rates.

  - Female patients had twice the response rates of male patients in two of the studies, and about the same response rate as male patients in the third study. This reviewer, in light of similar response rates in female and male MDS patients in the azacitidine trials, is not convinced that there is gender difference in response rate to decitabine.
  - Response rates were not analyzed by race/ethnicity, because more than 90% of the subjects were White.
  - Responses occurred in patients with or without prior therapy for MDS and in patients with *de novo* and with secondary MDS, although there were too few patients with secondary MDS or with prior therapy for MDS to make comparisons of response rates.
- Analyses of secondary endpoints revealed:
  - Decitabine treatment had no effect on overall survival.
  - Decitabine treatment resulted in decreased RBC and platelet transfusion requirements in transfusion-dependent patients, and decreased the risk of patients becoming transfusion-dependent.
  - Febrile neutropenia occurred more frequently in decitabine-treated patients than in supportive care patients.
  - Hematological Improvement rates (Complete Response plus Partial Response plus Hematological Improvement) were higher in decitabine-treated patients than in supportive group patients.
  - In Quality of Life analyses, decitabine-treated patients had statistically superior global health status, dyspnea and fatigue.
  - About 19% (9/48 patients with clonal abnormalities at baseline) had a major cytogenetic response (no abnormality) and 2% (1/48) had a minor cytogenetic response (≥ 50% reduction in abnormal metaphases) in the decitabine treatment arm. About one-half (8/15) of patients who had a CR or PR had a major cytogenetic response. About 6% (2/33) of patients in the supportive care arm had a major cytogenetic response.

Dosage regimen is appropriate, since controlled trial patients received 97% of the prescribed dose. Delays of treatment and dose reductions in subsequent cycles occurred in about one-third of patients.

Role in armamentarium: The efficacy of decitabine in MDS is similar to that of azacitidine as measured by response rate.

1.3.3 Safety

(Please see Executive Summary 1.1. The conclusions below were based on data as submitted).

- A total of 240 patients with MDS received decitabine at the same dose as specified in the NDA in the three primary studies. Decitabine was administered in cycles of 6 weeks, and the median number of cycles was 3, with some patients receiving up to 9 cycles.

- There were no deaths that were attributed to DAC toxicity, although thrombocytopenia aggravated by DAC treatment may have contributed to bleeding, including intracerebral hemorrhage. The number of deaths was greater in the supportive care arm than in the DAC treatment arm during the study period; however, the total number of deaths during the total observation period was about the same in both arms. Disease progression to AML and infection were the most common causes of death in both arms.
- Hematological adverse events (neutropenia, febrile neutropenia, thrombocytopenia, anemia and leukopenia) were prominently more common in the decitabine arm than in supportive care arm. Hematological adverse events did not decrease with successive cycles unless the patient had a response. Gastrointestinal disorders (nausea, constipation, diarrhea, vomiting, abdominal pain, stomatitis, dyspepsia and ascites) were more common in the decitabine arm than in the supportive care arm. They decreased after the first two cycles of decitabine therapy with appropriate medications. Fever, bacterial and fungal infections, painful joints or muscles, backaches, chest wall discomfort, headache, insomnia, confusional state, ecchymoses, pallor, erythemas, alopecias and skin disorders were also more common in the decitabine arm than in the supportive care arm. There were no greater than grade 2 hepatic or renal function abnormalities. Vital signs reflected general clinical condition rather than MDS or decitabine therapy.
- Adverse events (thrombocytopenia, lymphadenopathy, neutropenia, pneumonia, *M. avium* infection, cardiac arrest, and elevated liver function tests) led to discontinuation of decitabine therapy in 10% of patients, and of withdrawal from the supportive care arm in 2% of patients (because of COPD and of dyspnea). About 19% of patients had dose delays, about 5% of patients had dose reduction, and about 11% of patients had dose reduction and dose delay.
- There are no safety data on pregnant or lactating women (who were excluded from enrollment), or on infants and children (MDS is very rare in childhood) in this submission.
- Overdose data is available from older studies in which patients were treated with several-fold higher decitabine dosages. The main toxicity was hematological.
- The most common adverse events due to decitabine overlap those of MDS, making attribution and safety evaluation difficult. Decitabine therapy is effective in eliminating or reducing transfusion dependence, and the adverse events appear to be tolerable for the achievement of this goal.

1.3.4 Dosing Regimen and Administration

Decitabine is administered by a 3-hour intravenous infusion at a starting dose of 15 mg/m^2 every 8 hours for three days every 6 weeks.

1.3.5 Drug-Drug Interactions

Severe thrombocytopenia was reported in a patient receiving decitabine and tamoxifen with bleeding and subdural hematoma. Antineoplastic agents appear to accentuate tamoxifen-associated thrombocytopenia, which has been reported with tamoxifen monotherapy as well.

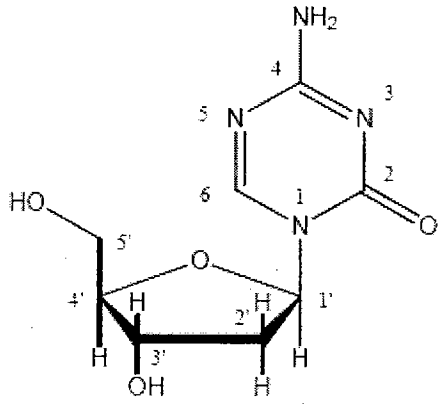
1.3.6 Special Populations

There is no information on patients with hepatic or renal impairment because they were excluded from the trials. There is limited information on patients of different races/ethnic backgrounds other than White.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

- Dacogen™ for Injection contains 5-aza-2'-deoxycytidine or decitabine (abbreviated as DAC in the rest of the review), an analogue of the natural deoxyribonucleoside 2'-deoxycytidine. In 5-aza-2'deoxycytidine the carbon at position 5 of the pyrimidine ring is replaced by a nitrogen (see Figure below).
- Dacogen™ for Injection is a white sterile lyophilized powder supplied in a clear colorless glass vial. Each vial contains 50 mg decitabine, potassium dihydrogen phosphate and sodium hydroxide. It is to be reconstituted with 10 mL of Sterile Water for Injection and then further diluted with 5% D/W, NS, or Lactated Ringer's for intravenous (IV) infusion. The final drug concentration is to be 0.1 – 1.0 mg/mL.
- The generic name is decitabine.
- The chemical name is 4-amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one.
- Proposed trade name is Dacogen™.



- It is a new molecular entity (NME).
- Pharmacologic class: decitabine is an antineoplastic agent. It is incorporated into DNA following phosphorylation to 5-aza-dCTP and is a specific inhibitor of the DNA methyltransferase enzymes. DNA methylation occurs after DNA replication and involves the transfer of a methyl group from S-adenosyl-methionine to the position 5 of the deoxycytidine residues. These reactions are carried out by DNA-methyltransferases I, IIIa

and IIIb. Decitabine is able to inhibit DNA methylation by the formation of a stable complex between the DNA methyltransferase enzymes and 5-aza-cytosine-substituted DNA. In general, methylation of DNA represses gene expression, whereas demethylation results in gene activation. In mammalian cells, about 5% of the doxycytidine residues in DNA are present as 5-methyldeoxycytidine. By inhibiting DNA methylation, decitabine prevents DNA hypermethylation of CpG islands associated with a variety of tumors and MDS. By hypomethylation of replicating DNA, decitabine induces neoplastic cell differentiation into normal cells. Decitabine also causes cell cycle arrest and apoptosis. Thus, it is both a cell differentiation inducing agent and a cytotoxic agent.

- Indication is treatment of patients with myelodysplastic syndrome including previously treated and untreated, de novo and secondary. The recommended dosing regimen is 15 mg/m^2 administered by continuous IV infusion over 3 hours repeated every 8 hours for 3 days every 6 weeks. Age restriction is not specified.

2.2 Currently Available Treatment for Indications

Vidaza™ (5-azacitidine) was approved on May 19, 2004 for a similar indication. The mechanisms of action of 5-azacitidine and of decitabine on the inhibition of DNA methylation are thought to be identical.

2.3 Availability of Proposed Active Ingredient in the United States

The product is not currently marketed in this country.

2.4 Important Issues with Pharmacologically Related Products

The pathophysiology of MDS overlaps to a great extent the most common toxicities of azacitidine and decitabine, which result from myelosuppression. Consequently, anemia, leucopenia, neutropenia, infections, thrombocytopenia, bleeding, hematomas and patechiae are common events with MDS and with treatment with azacitidine and decitabine. Gastrointestinal adverse events, such as anorexia, nausea, vomiting, diarrhea, and constipation are common during treatment with azacitidine and decitabine. Transient elevations of hepatic enzymes are common to both agents. Hepatic failure may develop in patients with pre-existing hepatic disease.
Overall response rates are approximately the same with decitabine and azacitidine.

2.5 Pre-submission Regulatory Activity

Background and Rationale: The controlled study protocol was submitted in compliance with Guidance for Industry, "Special Protocol Assessment" (May 2002) and as a result of the discussion held between SuperGen, Inc. and FDA representatives at the pre-NDA meeting held on February 6, 2004.

Regulatory History:
Decitabine (like azacitidine) was originally synthesized in mid-1960s in the Chechoslovakian Academy of Sciences as a potential therapeutic agent for cancer. The first publication in English on the effect of decitabine against leukemic and hematopoietic tissue in AKR mice dates from 1968 (Sorm F, Vesely J. Neoplasma 1968;15:339-43). The effect on DNA methylation and cellular differentiation date from 1980 (Jones PA, Taylor SM. Cellular differentiation, cytidine analogs and DNA methylation. Cell, 1980;20:85-93). The first clinical study was reported in 1981 (Rivard GE, Momparler RL, Demers J et al. Phase I study on 5-aza-2'-deoxycytidine in children with acute leukemia. Leuk Res. 1981;5:453-62). Decitabine was distributed since 1970s by NCI as an investigational agent in treatment of acute and chronic leukemias, MDS and sickle cell anemia. Pharmachemie became the original IND 33,929 holder.

On August 5, 1998, FDA met with Pharmachemie and discussed the development of decitabine in the treatment of MDS. The Agency indicated that a single phase 3 study supported by a single phase 2 study could be sufficient for an NDA in high risk patients. The Agency also commented that hematologic response (CR, PR) could be acceptable as a potential surrogate endpoint in high risk MDS patients and a randomized phase 3 trial might assess a composite endpoint.

On October 8, 1999 SuperGen acquired decitabine from Pharmachemie. On January 31, 2001, FDA met with SuperGen in an End of Phase 2 meeting regarding D-0007 phase 3 trial ("A randomized, open-label, Phase III trial of decitabine [5-aza-2'-deoxycytidine] versus Supportive Care in adults with advanced-stage myelodysplastic syndrome") design. SuperGen proposed a primary endpoint of Overall Response Rate (CR + PR) by the MDS Working Group Criteria. FDA indicated that a composite endpoint of "ORR and time to progression to AML (>30% blasts in the marrow) or death" would be required for full approval. The sponsor revised the protocol with the new primary endpoint, including a revision of sample size to allow an interim analysis following 45 events. The revised protocol (Amendment 1) was accepted by FDA on March 13, 2001. Amendment 2 on February 5, 2002 eliminated patient crossover and expanded the inclusion criteria from IPSS (International Prognostic Scoring System) High Risk and Intermediate-2 patients to also include Intermediate-1 MDS patients. Amendment 3 on July 18, 2002 included a retrospective review of bone marrows by an outside expert.

On April 25, 2003, the sponsor held a meeting with the Agency to discuss interim clinical results from the first 45 events. The goal of the NDA application was defined as follows:
1. Regular approval, or
2. Accelerated approval by response rate, with EORTC study (time to AML progression or death as primary endpoint) as phase 4 commitment.

The sponsor submitted a revised Statistical Analysis Plan (SAP), which proposed a co-primary endpoint of Overall Response Rate (CR + PR) or Time to AML or Death. The data generated in the Phase 3 trial (Study 0007) were to form the basis of this NDA, supported by two Phase 2 and several Phase 1 and 2 studies. Fast Track designation for decitabine was granted on May 12, 2003.

Orphan Drug Status was granted for decitabine in treatment of patients with MDS in the U.S. to Pharmachemie USA, Inc. on March 8, 1999. On November 22, 2000 Orphan Drug status was transferred to SuperGen, Inc. Orphan Drug status was granted in the European Union on February 14, 2003.

Other Relevant Background Information

Decitabine is at present not marketed in any countries. Marketing applications have not been filed except in the U.S.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Assays: Decitabine (abbreviated as DAC) was synthesized in 1964 (1), results of the first pre-clinical tissues were reported in 1968 (2), and of the first Phase I study, in 1981 (4). In the intervening years, four methods were employed to assay DAC: bioassay, HPLC, radiolabeled drug, and LC/MS/MS assay. Most recently, the sponsor developed a HPLC/mass spectroscopy method. The LC/MS/MS method was used in all studies sponsored by the sponsor.

Chemistry and Administration: DAC is [redacted] It is [redacted] The decomposition could be slowed at refrigerated temperature (2-8°C). For that reason the solution is made up fresh every 7 hours and infused IV over 3 hours. DAC is supplied in 20 mL vials containing 50 mg of decitabine as a lyophilized powder, which are stored at refrigerator temperature. It is reconstituted with 10 mL Sterile Water for Injection, USP and contains 5 mg of decitabine and 6.8 mg of KH_2PO_4 per mL. Next, the reconstituted decitabine solution is diluted to 50 – 100 mL pre-chilled normal saline, lactated Ringer's or 5% D/W.

3.1 CMC and Product Microbiology

DAC, an [redacted] processed lyophilized powder, will be manufactured at Pharmachemie B.V. in Haarlem, The Netherlands. Product Microbiology review was completed and entered into DFS on July 18, 2005. NDA 21-790 is recommended for approval based on microbiological product quality. No deficiencies were identified based upon the information provided.

3.2 Animal Pharmacology/Toxicology

Acute and chronic toxicity. The original sponsor (Pharmachemie B.V.) conducted a series of toxicology studies early in the decitabine development program. These included single dose toxicity studies in Swiss mice and in AKR/BALB/c mice, and repeat dose toxicity studies in rabbits (decitabine was administered in the same regimen as in clinical studies, a 3-hour IV infusion every 8 hours for 3 consecutive days every 6 weeks for 4 cycles) and in rats. Other repeat-dose toxicity studies were conducted in mice (decitabine was infused for 5 days every 4 weeks) and in dogs. Dogs were found to be more sensitive to decitabine than mice or rats, because of low expression of cytidine deaminase, the primary enzyme responsible for decitabine

degradation in mammals. The main toxicities in all studies were bone marrow depletion and consequent pancytopenia, and enteropathy due to loss of integrity of intestinal mucosa.

Mutagenicity and Genotoxicity. DAC did not produce mutations in the Ames Salmonella/microsome test, or in CH3/10T1/2, V79, and CHO cells. Increased mutation frequency was produced by DAC in L5178Y mouse lymphoma cells, and in *E-coli lac-I* transgene in colonic DNA in DAC-treated mice. DAC was clastogenic in the human pro-B cell line FLEB14 and in the broad-bean *Vicia faba.* DAC was genotoxic in the Drosophila somatic mutation and recombination test (SMART). These data lead to the conclusion that DAC has genotoxic potential.

Teratogenicity. DAC caused axial and cranial malformations, digital abnormalities, and effects on long bones in fetuses of mice and rats. DAC caused fetal absorption in rats. *In utero* exposure to DAC resulted in teratogenesis, reduced fetal size, and decreased post-partum growth rates. *In utero* exposure to DAC results in decreased fertility, primarily in males, probably due to testicular atrophy, as well as behavioral and neurologic changes. Thus, DAC is a teratogen and adversely affects reproductive performance.

Carcinogenicity. A formal carcinogenicity evaluation has not been performed. DAC is not listed as a carcinogen in the 11th Report on Carcinogens by the National Toxicology Program (2004). Published evidence (in abstract form) is conflicting. Fisher rats treated for 12 months with DAC and tetrahydrouridine (to reduce DAC degradation) had no increased incidence of tumors. But Sprague-Dawley rats treated with DAC 3x/week for 86 weeks showed dose-related increases of tumors. DAC administered with a goitrogen to mice increased thyroid tumor incidence. However, DAC has also been used in cancer chemoprevention in mice. It reduced the incidence of intestinal polyps, and of chemically induced lung cancers. Toxicology review by the Agency found these findings (published mainly in abstract form) inconclusive.

QT prolongation. Drug effects on QT interval were not studied.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical Efficacy Trials (n = 253 patients treated with decitabine)

- D-0007: A Randomized, Open-Label, Phase III Trial of Decitabine (5-Aza-2'-Deoxycytidine) Versus Supportive Care in Adults with Advanced-Stage Myelodysplastic Syndromes
- PCH 97-19
- PCH 95-11

Additional Safety Data (n = 181 patients treated with decitabine)

- PCH 95-05 Differentiation Therapy with 5-Aza-2'-Deoxycytidine for Myelodysplastic Syndromes
- PCH 95-4 (Compassionate use) MDS
- 91-02 Phase II MDS
- 91-01 Phase II MDS
- 88-01 Phase I/II AML/MDS
- 79-02 Phase I/II Pediatric study, acute leukemia
- 79-01 Phase I/II Pediatric study, acute leukemia

4.2 Tables of Clinical Studies

Copied below is sponsor's Table 1 of Larger Phase II/III Studies and of older Phase I/II Studies. The D-0007 is the controlled Phase III trial that is the registration trial, supported by two single-arm trials. The older smaller trials for various indications are included in the safety evaluation.

Study ID	PI Location	Study Start Study Status	Design Control Type	Study and Control Drugs Dose, Route, and Regimen	No. of Subjects by Arm Entered/ Completed	Gender (M/F) Age Range (Years)	Diagnosis
Larger Phase II/III studies							
12-0007	Multi-center-USA	May 2001 complete	Phase III, randomized, open-label, Dacogen versus supportive care in adults with advanced-stage myelodysplastic syndrome	Dacogen IV 15mg/m² over 3-hr. t.i.d x 3d q6 weeks + Supportive Care Vs Supportive Care Alone	80/83 81/81	59M/30F 31-85 57M/24F 30-82	MDS
PCH95-11	Multi-center-Europe	April 1996 complete	Phase II multi-center, single agent Dacogen in patients with myelodysplastic syndromes	IV 15 mg/m² over a 4-hr period. q8h. x3d. q 6 weeks	66/66	46M/20F 37-84	MDS
PCH97-19	Multi-center-Europe	August 1997 complete	Compassionate-use Dacogen in patients with myelodysplastic syndromes	IV 15 mg/m² over a 4- hr period. q8h. x3d. q 6 weeks	98/98	72M/26F 51-87	MDS
Older Phase I/II Studies							
PCH88-08	Multi-center- Italy	1987 complete	Open-label, single-arm Phase I-II single-agent Dacogen in patients with AML and MDS (untreated or unresponsive to conventional treatment)	AML: starting at 30 (changed to 60) escalating to 170 mg/m² over 4-hr t.i.d x3d, q 4 weeks. MDS: starting at 15 escalating to 60 mg/m² t.i.d over 4-hr t.i.d x3d, q 4 weeks.	38/38 (25 AML, 8 MDS, 5 CML	17M/21F 53-83	AML/MDS/CML

Review Strategy

The review included:

- A survey of current literature on diagnosis, classification and treatment of MDS, using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed
- Review of the current recommendations of international working groups (FAB and IPSS) to standardize prognostic and response criteria for MDS
- Review of articles in medical literature describing the trials submitted with this NDA
- Review of summaries of Chemistry, Pre-Clinical Pharmacology/Toxicology, Clinical Pharmacology, and of experience in humans
- Review of the Sponsor's Clinical Overview of the trials submitted with this NDA. The primary review focus was the controlled Phase III trial, with supporting Phase II trials examined for consistency
- Review of supporting tables and data listings for various aspects of the trial and for evaluation of Sponsor's claims
- Review of patient narratives in selected cases
- Consultations with Pharmacology and Statistics reviewers
- Requests for additional information from the Sponsor
- Review of Division of Scientific Integrity consultation
- Formulation of conclusions and recommendations, and
- Evaluation of proposed labeling changes, and revision of these changes.

4.3 Data Quality and Integrity

The Agency's Division of Scientific Investigations audited the two largest sites of patient enrollment in the randomized D-0007 trial. The sites were chosen strictly on the basis of size (34 and 20 patients, respectively) and not for any other reason, such as information from other sources regarding data quality or an unusual preponderance of patients with treatment responses. No single site reported an unexpectedly large number of responders to treatment. The DSI report may be viewed in its entirety in the DFS. In brief, **the FDA investigators concluded that the data from both sites are unreliable.**

The FDA investigator reviewed the records of 12 of 34 randomized subject records at the Moffitt Cancer Center in Tampa, FL. The key findings were:

- Transfusion records were inadequate or inaccurate for 6 subjects. The numbers of transfusions recorded in source documents, CRFs, and data listings did not match. In two decitabine-treated patients some of the PRBC and platelet transfusions recorded in source documents were not recorded or recorded incorrectly in CRFs and data listings. In four patients PRBC and platelet transfusions in CRFs and data listings were not found in the

source documents. *(Reviewer: The sponsor subsequently responded [on August 16, 2005] that the source documents are available for these patients.)*

- Decitabine infusion records did not include durations of infusions (end times missing) for multiple doses in six subjects.
- Six subjects did not have protocol-specified weekly CBCs; thus, bone marrow function could not be assessed at those time periods.
- Pneumonia in one subject was not reported. SAEs were reported belatedly to IRB or the sponsor in five instances.
- Infusion times were longer than 3 hours in two subjects, and intervals between infusions were either less than 8 hours (6.75-7.0 hours) or greater than 8 hours (9.0-9.5 hours).

Another FDA investigator reviewed the records of 11 of 20 randomized subject records at Washington University in St. Louis, MO. The key findings were:

- Transfusion records in 3 subjects were inadequate or inaccurate. Transfusions listed in source documents were not recorded on the CRFs or in the data listings in two subjects, while source documents could not be located for 17 of 28 PRBC and platelet transfusions described in the data listing of the third subject. *(Reviewer: The sponsor subsequently responded [on August 16, 2005] that source documents are available for the third subject, and that transfusions did not need to be recorded for one subjects before 8 weeks prior to study entry. That leaves only one subject with inadequate transfusion documentation.)*
- Five subjects were enrolled in the trial in spite of meeting protocol exclusion criteria.
- CBCs and bone marrow examinations were not performed as specified by protocol in 6 patients.
- Decitabine infusions in 5 patients lasted longer than specified, did not have start or stop times, or their descriptions in the source documents and the CRFs did not match.
- Some transfusion and adverse event data in CRFs were prepared retrospectively.

Overall assessment by DSI, based on the above observations, is that the data collected at the above two sites are unreliable.

- Transfusion documentation was inadequate and inaccurate.
- CBCs and bone marrow assessments were not performed as specified in the protocol.
- Five subjects that met the exclusion criteria were enrolled at one site.
- Decitabine infusion times were longer than recommended in some subjects. This is important because of the instability of decitabine in aqueous solutions.

Reviewer's Note: The above report on data from the two largest patient enrollment sites in the pivotal controlled trial casts doubt on the reliability of data from other, perhaps all, sites in this submission. Clearly, the sponsor did not supervise data collection and did not carry out verification of collected data. Transfusion record (in 3/23 study subjects) and CBC monitoring deficiencies are especially troublesome in the assessment of efficacy, since the response rates and clinical benefit are based on these data.

4.4 Compliance with Good Clinical Practices

- The trials in this NDA were conducted in compliance with Office of Human Research Protections (OHRP), DHHS, and FDA Good Clinical Practice (GCP) regulations governing research in human subjects.
- The controlled trial took place at 25 investigational sites (24 in the U.S., 1 in Canada). The study protocol, subsequent amendments, patient information and written informed consent forms were approved by each IRB. The clinical protocol was performed in conformance with SuperGen, Inc., standard operating procedures, applicable FDA regulations (21 CFR 50, 54, 56, and 312), Therapeutic Products Directorate-Canada, and ICH Guidelines for expedited reporting of adverse events (ICH E2A) and for conducting research in according with Good Clinical Practices (ICH E6, September 19, 1997). *Reviewer's Note: See the above section on Data Quality and Integrity.*
- The study protocols and amendments, sample informed consent documents, and all other study-related documents were submitted to Independent Ethics Committees and/or Institutional Review Boards of the participating centers for review and written approval. All IECs/IRBs were duly constituted and operated in accordance with DHHS policy as described in 45 CFR 46.115 and prevailing federal requirements. Copies of the Independent Ethics Committees' approval letters were submitted to the Sponsor before enrollment of any patients. The list of all committees of the study sites, with names of the committee Chairpersons, is included in the submission.
- Written informed consent, which was in compliance with the Declaration of Helsinki and written in conformance with 21 CRF 50 and ICH E6, was obtained from each patient before enrollment in the study. The rationale and goals of the study, procedural details, and potential hazards involving adverse reactions were explained to the patients. Each patient was assured that he or she was free to withdraw from the study at any time.
- Patient confidentiality was ensured by assigning to each patient an identification number that was used in the electronic case report forms (eCRF) in place of the patient's name.
- Representative samples of the informed consent form and of eCRF were included in the submission.

4.5 Financial Disclosures

The sponsor submitted Form FDA 3454 certifying that it had not entered into any financial arrangements with the listed clinical investigators (Box 1 checked), signed by Karl Mettinger, MD, PhD, Senior VP and Chief Medical Officer on October 28, 2004.

Certification that no debarred persons had participated in any capacity was signed by Audrey F. Jakubowski, Ph.D. on May 27, 2004.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

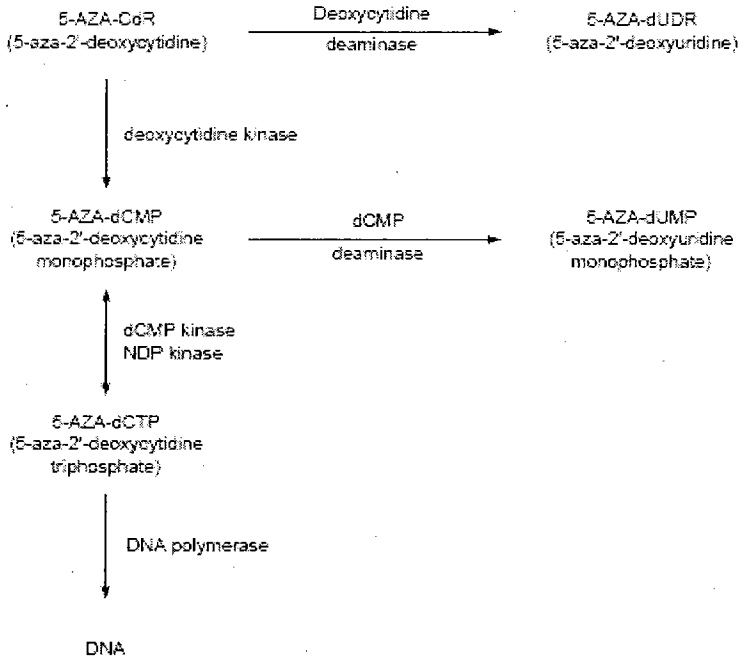
Mechanism of Action: In vivo, DAC is sequentially phosphorylated to mono-, di-, and triphosphate, which is incorporated into DNA in place of deoxycytine and binds covalently to DNA methyltransferases, thereby inhibiting DNA methylation. DAC-containing DNA is also cytotoxic as an S-phase specific agent to proliferating cells.

Metabolism: DAC is administered IV, because the oral bioavailability in mice was only 9% and intraperitoneal bioavilability was only 41%. Upon uptake by cells, DAC is rapidly degraded to 5-aza-2'-deoxyuridine, which is not cytotoxic, by hepatic cytidine deaminase (this enzyme is also found in other cells, but the rate of elimination of DAC is dependent on the amount of cytidine deaminase present in the liver). Renal excretion of DAC is <1% of dose administered in humans, indicating that metabolism is the major form of elimination. CYP 450 enzyme system is apparently not involved in DAC metabolism, eliminating this system as a source of drug interactions. Human plasma protein binding of DAC is <1%; hence, there would be no drug-drug interactions related to plasma protein binding. A schema of DAC metabolism is shown in sponsor's Figure 1.

Dosing: The dosing was developed to achieve concentrations of DAC in plasma that were shown to be cytotoxic in vitro against human tumor cell lines. In addition, it was shown in vitro that short-term exposure to DAC was ineffective, while long-term exposures (e.g. 24 hours) resulted in cytotoxicity. In L1210 cells, a minimum concentration of 0.5-1.0 µg/mL for 24 hours was required for maximum cell kill. In animals, 12-hour exposure was best for maximum cell kill without excessive toxicity. In human HL-60 myeloid leukemia cells, >80% cell kill was achieved with a concentration of 0.1 µg/mL for 48 hours.

Additional considerations were S-phase cycle specificity of DAC, and its ineffectiveness to block progression through the cell cycle. Initially, infusions of doses up to 100 mg/m^2 were shown to result in plasma concentrations of 0.4 µg/mL after a 1-hour infusion, 0.1-04 µg/mL after a 40-hour infusion, and 0.36-0.76 µg/mL after a 40-60 hour infusion of 1 mg/kg/hour.

Figure 1 Metabolism of Decitabine



Pharmacokinetics: In man, the distribution phase has an initial half-life of 7 minutes and a terminal elimination half-life of 10 to 35 minutes. The volume of distribution is 4.6 L/kg and total body clearance is also high, about 126 mL/min/kg.

DAC C_{max} was 0.44 mg/mL when administered at 100 mg/m^2 over one hour. When given at 100 mg/m^2, DAC total body clearance exceeds hepatic blood flow (1400 mL/min); therefore, extra-hepatic metabolism accounts for much of drug clearance. Urinary excretion of unchanged DAC is low, ranging from <0.01% to 0.9% of the total dose. Six patients with lung, esophageal, or pleural cancers underwent PK studies. There was low inter- and intra-patient variability in the disposition of DAC.

Interaction of DAC with cytochrome P450 enzyme systems was not studied, but like azacitidine and other nucleosides, DAC is unlikely to be an inducer or an inhibitor of these enzymes. Drug-drug interaction studies have not been carried out.

5.2 Pharmacodynamics

DAC induces hypomethylation of genes that are hypermethylated in carcinogenesis. As a result of hypermethylation at gene promoter CpG sequences, tumor suppression genes are inhibited, angiogenesis genes are expressed, metastasis genes are expressed, and DNA repair genes are inhibited. As a result, cell growth and proliferation are dysregulated and carcinogenesis results.

Specific cancers have specific CpG sequences hypermethylated. In MDS, the $p15^{INK4B}$ gene is frequently and selectively hypermethylated (about 80% of patients [19/23]) (34).

DAC is at least ten-fold more cytotoxic in vitro than azacitidine, possibly because DAC is incorporated only into DNA, while azacitidine is incorporated into both RNA and DNA. Both compounds inhibit DNA methyltransferase activity by covalently binding the enzyme to DAC incorporated into DNA. Demethylation of the p15 gene in MDS has been reported to be associated with clinical response in (37). Thus, demethylation of the $p15^{INK4B}$ gene may be a pharmacodynamic marker of decitabine activity.

Resistance to DAC may be correlated with levels of DNA methyltransferase, since resistant cells bind the same amount of DAC as non-resistant cells.

At high doses DAC is directly cytotoxic to malignant cells and also to normal cells. Lower doses were used in the MDS treatment schedules than in previous schedules in treatment of solid tumors.

5.3 Exposure-Response Relationships

A considerable body of data exists on high-dose DAC therapy for solid tumors and AML. These data are not germane to this NDA, in which the lowest possible doses that are sufficient for inhibition of DNA methylation and for the minimum amount of cytotoxicity are used.

6 INTEGRATED REVIEW OF EFFICACY

Prior to reading this summary of the sponsor's data please refer to section 4.3 Data Quality and Integrity.

6.1 Indication

Decitabine is indicated for treatment of patients with myelodysplastic syndrome (MDS), including previously treated and untreated, *de novo* and secondary MDS, of the following subtypes:

- By FAB classification: refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia

- By IPSS classification: High Risk, INT-2, and INT-1.

6.1.1 Methods

Nosology of Myelodyslastic Syndrome (MDS). A number of chronic diseases of bone marrow dysfunction, characterized by decreased counts of one or more blood cell types and/or an increase in bone marrow blasts, have been grouped into a syndrome called MDS. Among them are what were formerly called "pre-leukemia", "smoldering leukemia", "refractory anemia", and "ring sideroblast anemia".

In primary MDS, the etiology is unknown. Secondary MDS may have been caused by prior chemical or radiation injury, chemotherapy, and radiotherapy. Secondary MDS generally has a poorer prognosis than primary MDS. Both primary MDS patients and secondary MDS patients have been enrolled in trials supporting this NDA.

Primary MDS has been reported in all age groups, with the highest prevalence in those over 60 years of age. Presenting symptoms depend on the cell line affected. Anemia results in fatigue, weakness, pallor, dyspnea, angina pectoris, heart failure; thrombocytopenia, in easy bruising, epistaxis, gingival bleeding, patechiae; neutropenia, in bacterial infections, particularly respiratory and dermal. Hepatosplenomegaly occurs in 10% to 40% of patients. Transformation to acute myelogenous leukemia (AML) occurs in up to 40% of patients with MDS. Most of MDS patients die from bleeding or infection.

Several classifications of MDS have been proposed. The most commonly accepted is the original FAB (French-American-British) classification (Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C. Proposals for the classification of the myelodysplastic syndromes. Brit J Haematol 51:189, 1982) in which 5 subtypes of MDS are described and characterized as follows:

- RA (Refractory anemia): <5% blasts in the bone marrow (BM), ≤1% blasts in peripheral blood (PB);
- RARS (RA with ringed sideroblasts): RA + ≥15% ringed sideroblasts in BM;
- RAEB (RA with excess blasts): 5% - 20% blasts in BM, <5% blasts in PB;
- RAEB-T (RAEB in transformation): 21% - 30% blasts in BM, >5% blasts in PB; and
- CMMoL (Chronic myelomonocytic leukemia): ≤20% blasts in BM, <5% blasts in PB, absolute monocytosis (>10^9/L).

Syndromes that affect only the RBC line are RA and RARS.

- RA is characterized by PB findings of macrocytic anemia, reticulocytopenia, and normal leukocyte and platelet counts. In BM, the erythroid line is megaloblastic and hyperplastic. Myeloid and megakaryocytic lines are normal. Dysplasia is minimal.
  - Prognosis: median survival is 3 to 6 years; transformation to AML is rare.
  - Percentage of MDS patients presenting with this syndrome: 20% to 30%.
  - Mainstay of treatment: RBC transfusions.

- RARS differs from RA only in that at least 15% of erythroid precursors are ringed sideroblasts.
  - Prognosis: same as RA.
  - Percentage of MDS patients presenting with this syndrome: 2% to 5%.
  - Mainstay of treatment:. RBC transfusions.

Syndromes that affect all blood cell lines are the following.

- RAEB is characterized by RA and increased blasts (up to 20%) in the marrow (upper limit of normal is <5%).
  - Prognosis: median survival is 6 to 9 months.
  - Progression to acute myelogenous leukemia (AML): in approximately 40% of patients.
  - Percentage of MDS patients presenting with this syndrome: approximately 33%.

- RAEB-T is RAEB with blasts in the marrow increased up to 21% to 30%.
  - Prognosis: median survival is 6 months or less.
  - Progression to AML: in approximately 60%.
  - Percentage of MDS patients presenting with this syndrome: approximately 25%.

CMMoL is the MDS syndrome that affects mainly monocytes.

- CMMoL is characterized by an increase in the number of monocytes in PB. Red cell precursors in BM appear normal, although a mild anemia may be present.
  - Prognosis: median survival is 14 to 18 months.
  - Progression to AML: can occur.
  - Percentage of MDS patients presenting with this syndrome: 15% to 20%.

Response Criteria in the Treatment of MDS. An International Working Group has published response criteria that should be used in clinical trials of MDS treatments (Cheson BD et al., 2000). These criteria describe four categories of responses to treatment and are briefly summarized below. *Note:* The 2000 Cheson et al. criteria specify that the response last a minimum of 2 months. The D-0007 trial was carried out with the 2000 Cheson et al. response criteria. The older Cheson et al. (1981) criteria do not specify this time requirement. The Phase II studies were carried out the older criteria.

- Altering Disease Natural History: Complete Remission [CR], Partial Remission [PR], Stable Disease [SD], Failure, Relapse after CR or PR, Disease Progression, Disease Transformation [to AML], Survival and Progression-free survival.

CR is defined as follows:
Bone marrow: Repeat bone marrow showing <5% myeloblasts with normal maturation of all cell lines, with no evidence for dysplasia.
Peripheral blood (values must last at least 2 months): Hgb > 11g/dL, ANC ≥ 1500/mm^3, platelets ≥ 100,000/mm^3 (patient not receiving erythropoietin, myeloid growth factor, or thrombopoietic agent), absence of blasts, absence of dysplasia.

PR is defined as follows:
Bone marrow: Blasts decreased by 50% or more over pretreatment, or a less advanced MDS FAB classification than pretreatment, normal maturation of all cell lines, without evidence of dysplasia.
Peripheral blood: As in CR.

- Cytogenetic Response: Major or Minor.
- Quality of Life: Improvement in physical, functional, emotional, social, and spiritual domains.
- Hematologic Improvement: Erythroid response, Platelet response, Neutrophil response [each either Major or Minor], Progression/relapse after Hematologic Improvement.

In addition, the Working Group defined the endpoints for clinical trials in MDS (Overall Survival, Event-free Survival, Progression-free survival, Disease-free survival, and Cause-specific Death).

New revisions of MDS classifications have appeared. The 1999 WHO Classification lists RA, RARS, refractory cytopenia with multilineage dysplasia (RC + Dys), RAEB I and II, del (5q) syndrome, and MDS unclassifiable. RAEB was split into two subtypes on the basis of percentage of blasts in the marrow, RAEB I (<10% blasts) and RAEB II (>10% blasts). CMMoL and RAEB-T patients were excluded. RAEB-T patients were re-classified as AML, and the threshold for blasts in AML was decreased from 30% to 20%. CMMoL is now included among chronic myelogenous leukemias. The WHO classification has so far not been met with universal agreement.

Another classification system (International Prognosis Scoring System, IPSS) by the International MDS Study Group (Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Vallespi T, Hamblin T, Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G and Bennett J. International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes. Blood 89: 2097-88, 1997) aims to classify MDS by prognostic factors, and less by morphological demarcation of subgroups. The risk variables used for the prognostic model were bone marrow blast percentage, number of cytopenias, and cytogenetic subgroup. These three risk factors were significant variables for survival and evolution to AML. By combining the risk scores for these 3 major variables, patients were stratified to 4 risk groups with scores being 1) Low, score 0; 2) Intermediate-1 (INT-1), score 0.5 to 1.0; Intermediate-2 (INT-2), score 1.5 to 2.0; and High, score ≥ 2.5. The relationship of IPSS risk group, IPSS score, and median survival is shown in sponsor's Table 2. IPSS scoring requires cytogenetic analyses.

Table 2 International Prognostic Scoring System (IPSS) for MDS

Risk	Median Survival (Years)	IPSS Score
Low	5.7	0
Intermediate–1	3.5	0.5–1.0
Intermediate–2	1.2	1.5–2.0
High	0.4	≥2.5
Reference: 23		

Phase III Controlled Trial D-0007

Patients in the controlled trial in this NDA consisted of all 5 FAB subgroups and of High-risk, Intermediate-2 (INT-2) and Intermediate-1 (INT-1) subgroups of the IPSS classification.

Study Objectives.

- The overall objective of this multi-center study was to demonstrate the superiority of decitabine injection over supportive care for treatment of adults with MDS.
- The co-primary efficacy endpoints were 1) the percent of patients achieving a Complete or Partial Response (CR + PR) during randomized treatment and 2) Time to AML or Death.
- The secondary objectives included
  - Overall survival
  - Transfusion requirements
  - Rates of febrile neutropenia
  - Percent of patients achieving Hematological Improvement (CR + PR + HI)
  - Quality of Life
  - Cytogenetic Responses and Safety.

6.1.1 General Discussion of Endpoints

The Phase 3 controlled trial (D-0007) was the major source of data for the efficacy review. The single-arm trials and literature reports were used to support the results of the controlled trial.

The choice of endpoints is discussed above in the Regulatory History (Section 2.5).
Primary endpoint: The co-primary endpoints were

- Overall Response Rate (CR + PR) as defined by the MDS International Working Group criteria, and
- Time to AML or Death.

Secondary endpoints:

- Survival
- Transfusion Requirements

- Improvement (CR + PR + Hematological Improvement)
- Quality of Life, and
- Cytogenetic Response.

6.1.2 Study Design

The study design of the controlled D-0007 trial meets the regulation on adequate and well-controlled studies (21 CFR 314.126) and the results provide a reasonable assessment of benefit.

This was an open-label, parallel-group, randomized trial of 170 adult patients with histologically confirmed MDS who met IPSS criteria for INT-2 or high-risk categories, and later, as allowed by Protocol Amendment 3, patients meeting the INT-1 risk category.

Given that DAC is administered IV every 8 hours for 3 days, a double-blind study was not possible. A blinded review of all bone marrow aspirates and biopsies was performed by an expert hematopathologist.

Study Entry Procedures

- Baseline history, physical examination, bone marrow aspirates, biopsies, and cytogenetics samples, CBC, serum chemistries, serum hCG, and the EORTC Quality of Life questionnaire completed.
- Randomization to decitabine or Supportive Care treatment arms was 1:1 using a centralized, call-in randomization process. The Biometrics and Statistics Department of SuperGen supervised each randomization. Patients were stratified by study center, IPSS classification and type of MDS (*de novo* or secondary).
- Baseline Demographics and Other Patient Characteristics are shown in Sponsor's Table 7 below in Selection of Study Population (6.1.2.5).

Treatment Procedures

- Both treatment groups received standard supportive care, including PRBC or platelet transfusions, erythropoietin, thrombopoietin, prophylactic antibiotics, and hospitalization.
- Patients in the DAC arm received DAC 15 mg/m^2 injection as nine 3-hour infusions over 3 days (one infusion every 8 hours for 3 days) per 6-week cycle administered in the hospital, clinic or through home infusion care.
- Selection of doses: During the development of DAC a variety of different doses and schedules had been explored in treatment of various solid tumors and hematologic malignancies (typically 200-1000 mg/m^2 per cycle). The dose and schedule in the 3 trials submitted in this NDA was derived from a Phase I/II dose-escalation study in 38 patients with AML, CML or MDS (PCH 88-01). The subsequent Phase II studies (PCH 95-11 and PCH 97-19) used the lowest dose level in MDS patients (15 mg/m^2 administered over 4

hours every 8 hours for 3 days) in PCH 88-01 to reduce myelotoxicity and to allow for bone marrow recovery.

- Every 6 weeks patients received a medical H & P, CBC, serum chemistries, and Q of L questionnaire. Cycles were repeated once the patient's hematologic parameters returned to pretreatment or to normal levels.
- Criteria for dose reduction or cycle delay: if blood count recovery took >6 weeks, but <8 weeks, DAC was held for up to 2 weeks and the dose was reduced to 11 mg/m^2 every 8 hours; if blood count recovery took >8 weeks but <10 weeks, patient was assessed for disease progression by bone marrow aspirate; if there was no progression, DAC was held for 2 more weeks and the dose was reduced as above. If the following non-hematological toxicities occurred, DAC treatment was not restarted until the toxicity resolved: serum creatinine > 2 mg/dL, SGPT, serum bilirubin > 2 x ULN, or active uncontrolled infection.
- Every 12 weeks a BM aspirate and biopsy were performed to evaluate response to treatment. After any 2 cycles, DAC arm patients were taken off study if they demonstrated progressive disease (PD), as defined by the MDS Working Group. Other patients were continued on treatment for a maximum of 10 cycles.
- At the end of study, the final bone marrow aspirate and biopsy, CBC, serum chemistries, hCG and Q of L questionnaire were administered.
- Crossover: Patients in the Supportive Care arm who progressed to AML or experienced rapidly progressive disease were initially allowed to crossover and receive DAC. This practice was stopped with Amendment 2 (by that time 3 patients had crossed over). Subsequently, such patients were permitted to participate in a different Phase II protocol of DAC for AML.

Interim Analysis Rationale and Steps Taken to Minimize Bias

- The original design of the protocol used Overall Response (CR + PR) as the single primary endpoint. At FDA's recommendation, the primary endpoint was changed to Time to AML or Death. A minimum sample size of 80 patients per group provided 80% power to two-sided significance level of 0.05 and allowed one interim analysis after 45 events. The sample size was based on a projected 6-month accrual period and a total study period of 24 months. The median times to AML progression or death were estimated in the DAC arm and the supportive care arm to be 22 and 12 months, respectively. These assumptions were based on the results of a randomized trial of azacitidine vs. best supportive care in MDS (Silverman LR, Demakos EP, Peterson B, Odchimer-Reissig R, Nelson D, Kornblith AB, et al. A randomized controlled trial of subcutaneous azacitidine (Aza C) in patients with the myelodysplastic syndrome (MDS): A study of the Cancer and Leukemia Group B. In abstract form in: Proc Am Soc Clin Oncol 1998; vol. 17, abstract No. 53, and in final form: J Clin Oncol 2002;20:2429-2440). Review of the trial results by the Agency did not support these authors' conclusion that azacitidine extended the time to AML or Death (see Vidaza™ approval summary).
- Selection bias was minimized by a centralized all-in randomization process.

- Evaluation bias was limited by the use of a blinded central review of all bone marrow aspirates and biopsies in addition to the initial diagnoses by local pathologists. (Hematologic classification inter-pathologist concordance is 67% in MDS).

Treatment Compliance and Drug Accountability

- The investigator or study site pharmacist kept a drug accountability log and drug preparation log. Each administered dose was recorded in the patient's CRF.
- Drug accountability procedures were carried out according to SuperGen protocols.

Selection of Study Population

Inclusion Criteria:

- Diagnosis of MDS (de novo or secondary) of any of 5 FAB classifications and IPSS >0.5, as determined by CBC, bone marrow assessment, and cytogenetics within 30 days of randomization.
- 18 years or older
- ECOG or WHO PS of 0 – 2
- Signed informed consent
- Adequate renal and hepatic function (creatinine $\leq$ 1.5 mg/dL, bilirubin $\leq$ 1.5 mg/dL, SGPT $\leq$ 2 x ULN)
- Not pregnant, adequate pregnancy prevention, not lactating.

Exclusion Criteria:

- AML or other progressive malignant disease
- Treatment with danazol, androgenic hormones, or colony-stimulating factors within 7 days of start of study
- Any investigational agent within 30 days prior start of study
- Uncontrolled cardiac disease, CHF, uncontrolled restrictive or obstructive pulmonary disease
- Active viral or bacterial infection
- Concurrent autoimmune hemolytic anemia or thrombocytopenia
- HIV serology
- Mental illness
- Not recovered from prior therapy toxicity; been off all chemotherapy for a minimum of 4 weeks (6 weeks for nitrosoureas and BMT)

Removal of Patients from Therapy or Assessments:

- Evidence of disease progression, per protocol, at any time during the study
- Transformation to AML
- Failure to achieve PR after 6 cycles of decitabine
- Failure to achieve CR after 8 cycles of decitabine

- Any CTC Grade 4 (life-threatening) non-hematological toxicity; or any Grade 3 (severe) non-hematological toxicity failing to improve within 10 weeks following a decitabine treatment cycle
- Failure to recover from prolonged cytopenia within 10 weeks after administration of a reduced dose of decitabine
- Patient's request to end study treatment
- Patient withdrew informed consent
- Supportive Care patients that progressed to AML or had rapid progression of disease qualified for AML protocol

Study Population: Demographic and Other Baseline Characteristics randomized to the two study arms are shown in Reviewer's Table below (from Sponsor's Table 7).

Reviewer's Table. Baseline Demographics and Other Baseline Characteristics

Demographic or Other Patient Characteristic	**Decitabine, N = 89**	**Supportive Care, N = 81**
Age, mean, median and (range) in years	69, 70 (31 – 85)	67, 70 (30 – 82)
Age stratification		
< 65 years (%)	23 (26%)	30 (37%)
65 – 74 (%)	42 (47%)	35 (43%)
75 - (%)	24 (27%)	16 (20%)
Gender : Male	59 (66%)	57 (70%)
Female	30 (34%)	24 (30%)
Race: White	83 (93%)	76 (94%)
Afro-American	4 (4%)	2 (2%)
Other	2 (2%)	3 (4%)
Weeks since MDS diagnosis		
Mean	86	77
Median	29	35
Range	2 – 667	2 - 865
Percent Blasts in BM		
Mean	11%	11%
Median	10%	9%
Range	[redacted]	[redacted]
Missing values	[redacted]	[redacted]
Type of MDS		
De novo MDS	77 (87%)	70 (86%)
Secondary MDS	12 (13%)	11 (14%)
Previous MDS Therapy*		
Yes	27 (30%)	19 (23%)
No	62 (70%)	62 (77%)
IPSS Classification		
INT-1	28 (31%)	24 (30%)
INT-2	38 (43%)	36 (44%)
High Risk	23 (26%)	21 (26%)

Table 6 Changes in Stratification Classifications

Reason	Dacogen N = 89* (%)	Supportive Care N = 81* (%)
Prior Chemotherapy for MDS changed to No	1 (1)	2 (2)
No Prior Chemotherapy for MDS changed to Yes	4 (4)	0 (0)
Prior treatment of Stratification Reassignments	**5 (6)**	**2 (2)**
Intermediate-2 IPSS changed to intermediate-1 IPSS	2 (2)	0
Intermediate-2 IPSS changed to high risk IPSS	3 (4)	2 (2)
Intermediate-1 IPSS changed to Intermediate-2 IPSS	0	1 (1)
High risk IPSS changed to Intermediate-2 IPSS	1 (1)	0
IPSS Stratification Reassignments	**6 (7)**	**3 (3)**
Total	**11 (12)**	**5 (6)**

* Two patients in the Dacogen arm and two patients in the Supportive Care arm had incorrect stratifications in both prior treatment of MDS and IPSS category.

Population Datasets:

- Intention-to-Treat (ITT) analysis included 89 patients randomized to DAC and 81 patients to supportive care, a total of 170 patients. All patients were included in the ITT analysis, including the 6 patients randomized to DAC arm who never received study drug.
- Evaluable Patient analysis included 56 patients in the DAC arm and 78 patients in the supportive arm, a total of 134 patients. The following categories of patients were excluded from the Evaluable Patient population.
    - Patients who were diagnosed as having AML at Baseline (9 DAC arm patients and 3 supportive care arm patients) by Dr. Bennett's expert interpretation of the bone marrow were excluded.
    - Six (6) patients randomized to DAC who did not receive study drug were excluded. One of these patients had progressive disease and was then ineligible, one was hospitalized with cellulitis, one was hospitalized with pneumonia, two withdrew consents, and one had AML.
    - Eighteen (18) patients in the decitabine arm who did not complete cycle 2 were excluded for the reason that these patients had less than an adequate number of treatment cycles to achieve a response.

Reviewer's note: The evaluable population consisted of about 63% of patients originally randomized to DAC and of 96% of the population originally randomized to supportive care.

Disposition of Patients: As shown in sponsor's Figure 2, approximately 60% of patients in each arm completed the study. The reasons for patient discontinuation from the study are shown in sponsor's Table 4.

Figure 2 Patient Disposition Between Treatment Arms

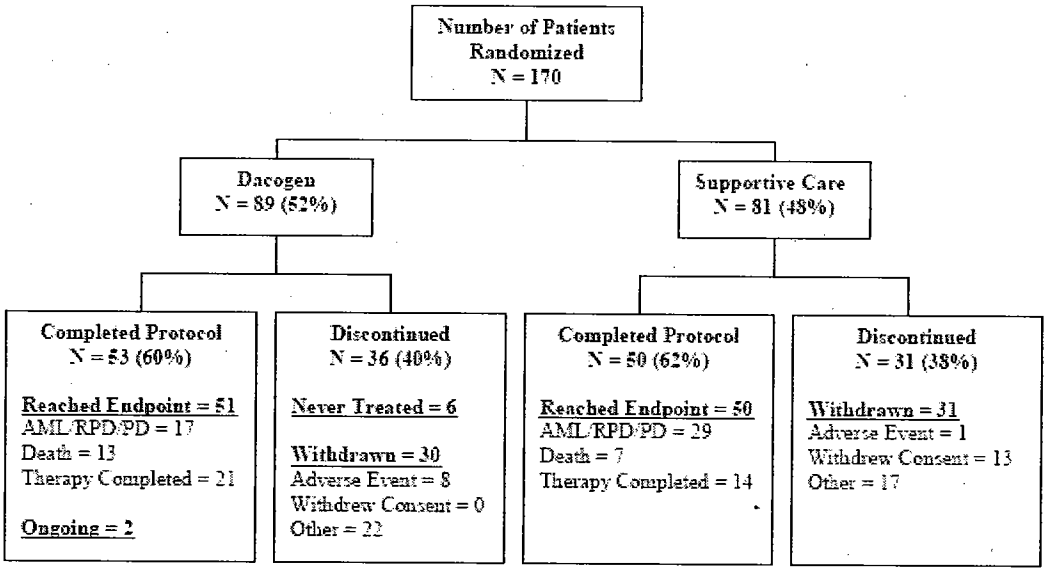


Table 4 Reasons for Patient Discontinuation from Study

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	5 (7)Σ	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.

Protocol Deviations: Only one patient entered the trial with a major protocol violation. This patient was randomized to DAC, but never received the drug. Most of the violations (21 in the DAC arm and 13 in the supportive arm) were minor laboratory values outside the protocol-specified range and patients who had experienced malignancy within 3 years of randomization. Eighteen violations in the DAC arm and 10 violations in the supportive care arm were waived. Patients with minor violations were not excluded from analyses.

Crossover Patients: Two of these patients with rapidly progressive disease crossed over to DAC arm and received DAC prior to development of AML. They were censored at the time of the first dose of DAC and the efficacy analysis only considered the time they spent in the supportive care arm. The third patient had already developed AML at the time of crossover. All 3 patients were considered for safety as having been exposed to DAC.

Treatment Compliance: 9 patients received fewer than 9 infusions per cycle for a variety of reasons (cytopenias [2], dose(s) not recorded [4], discontinued treatment [1], unknown reason [1]). A total of 300 cycles were administered with all 9 infusions out of a total of 309 cycles (this statistic includes 3 crossover patients who received all 12 cycles). Thus, there was 97% compliance with the number of doses per cycle.

Exposure to Decitabine or Supportive Care by Cycle: shown below in Sponsor's Table 9.

Table 9 Exposure to Dacogen or Supportive Care by Cycle

Cycle	Dacogen (N = 89)		Supportive Care (N = 81)	
	No. of Patients Completed	Percent of Patients Completed	No. of Patients Completed	Percent of Patients Completed
Cycle 1	83	93%	75	93%
Cycle 2	64	72%	61	75%
Cycle 3	47	53%	41	51%
Cycle 4	38	43%	30	37%
Cycle 5	27	30%	25	31%
Cycle 6*	23	26%	20	25%
Cycle 7	9	10%	6	7%
Cycle 8	7	8%	4	5%
Cycle 9	1	1%	1	1%
Cycle 10	0	0%	0	0%

* Two (2) patients randomized to Dacogen were still participating in the study following six cycles at database lock.

Number of cycles as reflected by investigator at End of Study. Six Dacogen patients were not treated and six Supportive Care patients withdrew before completion of the first 6-week cycle.

Efficacy Variables

Co-primary efficacy variables were:

- 1) Achievement of CR or PR, and
- 2) Time to AML or Death.
  - CR was defined per protocol as serial BM (bone marrow) aspirates showing < 5% myeloblasts without dysplastic changes. Peripheral blood evaluation must have met the following absolute values for at least 2 months: Hbg > 11 g/dL (without transfusions or erythropoietin use), ANC ≥ 1500/μL (without use of myeloid growth factor), platelets ≥ 100,000/μL (without a thrombopoietic agent); and no blasts or dysplasia.
  - PR was defined similarly to CR, except BM blasts were required to be decreased ≥ 50% over pre-treatment values, or for the patient to have less advanced MDS by FAB classification versus pretreatment.

- Date of AML conversion was based on the first date with a diagnosis of AML (≥ 30% blasts); but AML conversion could be based on CBC if no marrow was available (specific agreement between the sponsor and FDA on February 6, 2004).
- Death was authenticated by a death certificate.

- Statistical considerations:
  - The overall Type-1 error rate was maintained at a maximum of 5% by applying a Bonferroni correction. Statistical significance was determined using a one-sided O'Brien-Fleming boundary of α=0.0026 and α=0.024 at interim analysis (after 45 events) and at final analysis (after 92 events). A maximum p-value of 0.024 was required to establish statistical significance of response to DAC, using a two-sided analysis for either co-primary endpoint.
  - Progression to AML was first diagnosed by the local pathologist, then adjudicated by a blinded hematopathology expert, Dr. JM Bennett. Assessments of best hematologic response according MDS IWG criteria were made at the local investigative site, and then independently reviewed and adjudicated by Dr. Richard Leavitt.
  - The difference in the Overall Response Rate (CR + PR) between DAC and supportive care arms was analyzed using Fisher's Exact Test. The difference in Time to AML or Death between the two groups was analyzed using both the generalized Wilcoxon and log-rank (preferred by the Agency) tests. Time to AML or Death was measured from the date of randomization to the date on which AML or death was established. For patients lost to follow up, the study site searched the Social Security database to identify the death date.
  - Censoring Mechanisms in Analysis of Time to AML or Death: 1) patient was lost to follow-up or patient has not reached AML or Death event (censored at the date of the last visit or of last CBC), 2) crossed over from supportive care arm to DAC arm (censored on the date patient first received DAC), and 3) patient withdrew consent (censored on the date patient withdrew consent).

Secondary efficacy variables were:

- Survival (duration of time from randomization to death from any cause). Rate comparisons by log-rank and Wilcoxon analyses.
- Transfusion requirements (number and units of PRBC and platelets for each patient by date, pre-study and while on study), analyzed by descriptive statistics. Definitions/rules:
  - Baseline transfusion dependent: patient had one or more transfusions in the 8-week period prior to study
  - On study transfusion dependent: patient had one or more transfusions on study and was not transfusion-free for at least one 6-week period on study.
  - Transfusion independence for CR, PR, or HI response required no transfusions during an 8-week period.
- Febrile neutropenia episodes were reported under AEs. Analyzed by Fisher's exact test.
- Improvement (CR + PR + HI) was assessed by MDS IWG criteria, and analyzed by Fisher's exact test. HI (hematological improvement) had to be sustained in the absence of

cytotoxic therapy for 2 months. Described as major or minor, and by the number of cell lines affected (HI-E, HI- N, HI-P and combinations). The criteria are defined in the protocol.

- Quality of Life scores were assessed at baseline, at the end of each dosing cycle and at the end of treatment and computed by EORTC QLQ-C30 Scoring Manual (3rd edition). Significant differences were tested using Wilcoxon rank-sum test.
- Cytogenic Response was categorized as major (no detectable abnormality if pre-existing abnormality was present) and minor (≥ 50% reduction in abnormal metaphases). The relationships between CR + PR and cytogenetic responses were compared using tabular presentations and descriptive statistics.

Study Protocol Amendments

There were 4 protocol amendments. The first two amendments were implemented before the first patient was enrolled in the study on July 24, 2001. The amendments are shown in Reviewer's table below.

Reviewer's Table of Protocol Amendments to D-0007 Trial

No.	Date	Amendment
1	2.26.2001	In accordance with FDA recommendations at EOP2 meeting, primary efficacy endpoint was changed from Overall RR (CR + PR) to Time to AML or Death. Sample size recalculated. HI clarified by MGS IWG criteria. AML defined by FDA criterion (30% blasts) instead of WHO criterion (20% blasts), addition of prior MDS treatment and type of MDS as randomization strata.
2	6.4.2001	Elimination of crossover of patients. Sample size increased to 80 per group. (3 patients were allowed to cross over until a new trial DAC-SGI-011 started for such patients).
3	10.26.2001	INT-1 patients included to increase study enrollment and to gather experience with these patients.
4	4.24.2002	Only AML (30% blasts) patients in supportive arm could move to DAC-SGI-011 (no waivers for 20%-30% blasts), clarified criteria for prior therapy, decreased randomization strata to 3 (study center, IPSS class, previous chemotherapy for MDS).
Revised SAP	3.12.2004	Primary efficacy endpoint was changed to co-primary endpoints of ORR and Time to AML or Death (statistical methods described above).

6.1.3 Efficacy Findings

6.1.3.1 Co-Primary Endpoint: Overall Response Rate (CR + PR)

The combined percentage of CR and PR according to the Adjudicated Data Set was used to evaluate the Overall RR in the ITT and Evaluable Population analyses. To be classified as CR or

PR using MDS IWG criteria, the patient was required to be RBC transfusion independent for 8 weeks during the time of response.

ITT and Evaluable Population Overall Response Rates are shown below (from sponsor's Table 10).

ITT Analysis of Overall Adjudicated Response Rate (CR + PR)

Parameter	Dacogen	Supportive Care	p-values[1]
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[1]
Median time to (CR – PR) response (days) (Range)	89 (55-153)	(0)	–
Median Duration of (CR + PR) response (days)	266 (131-346)	(0)	–

Evaluable Population Analysis of Overall Adjudicated Response Rate (CR + PR)

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[1]
Median time to (CR – PR) response (days) (Range)	89 (55-146)	(0)	–
Median Duration of (CR + PR) response (days)	277 (131-342)	(0)	–

In the ITT analysis, 8 patients had CR and 7 had PR for an Overall Response Rate of 17% (15/89). In the Evaluable Population analysis, 6 patients had CR and 6, PR for an ORR of 21% (12/56). The median time to response was about 3 months (89 days, range 55 to 153 days); the median cycle to respond was Cycle 3. The duration of responses was about 9 months (about 270 days, range 131 to 342 days).

There were no responders in the Supportive Care arm. Hence, these findings were significant ($p < 0.001$ by two-sided Fisher's Exact Test).

Reviewer's Notes: Evidence for CR and PR responses is found in Appendices 16.2.6.28 (Listing of Pertinent Data for All Responders), 16.2.4.1 (Listing of Baseline Characteristics), 16.2.6.1 (Listing of Bone Marrow Evaluations), and 16.2.6.26 (Listing of Transfusions). Reasons for responses are listed in Reviewer's Table below by patient number and FAB subtype.

Reviewer's Table. Evidence for CR or PR

Patient number	*FAB subtype*	*Evidence for CR or PR*
0121-5011	*CMML*	*CR. Pancytopenia at baseline, not requiring transfusions, increased monocytes and granulocyte precursors in peripheral blood. CR due to normalization of CBC.*
0121-5065	*RAEB**	*CR. Bone marrow blasts decreased from 10% to 2%. Lost RBC transfusion dependence. CBC normalized.*
0121-5081	*RAEB*	*CR. Bone marrow blasts decreased from 12% to 1%. Lost RBC transfusion dependence. CBC normalized.*
0143-5036	*RAEB***	*CR. Bone marrow blasts decreased from 5% to 1%. Lost RBC and platelet transfusion dependence with normalization of CBC.*
1002-5123	*RA*	*CR. Pancytopenia corrected. (Not transfusion dependent pre-study).*
1002-5148	*RAEB*	*PR. Bone marrow blasts decreased from 6% to 3%. Lost RBC and platelet transfusion dependence.*
1003-5070	*RAEB-t**	*PR. Bone marrow blasts decreased from 28% to 4%. Not transfusion dependent at study entry.*
1003-5113	*RA*	*PR. Pancytopenia partially corrected. Lost RBC and platelet transfusion dependence.*
1004-5063	*RAEB-t*	*PR. Bone marrow blasts decreased from 26% to 3.6%. Not transfusion dependent at study entry.*
1006-5006	*RAEB*	*PR. Bone marrow blasts decreased from 17% to 1%. Lost RBC and platelet transfusion dependence.*
1007-5069	*RAEB**	*CR. Bone marrow blasts decreased from 19% to 4%. Lost RBC transfusion dependence. CBC normalized.*
1008-5060	*RAEB*	*PR. Bone marrow blasts decreased from 8% to 2%. Not transfusion dependent at study entry.*
1008-5134	*RAEB*	*PR. Bone marrow blasts decreased from 12% to 2%. Lost RBC and platelet transfusion dependence.*
1032-5067	*RA*	*CR. Normalization of CBC. Lost RBC transfusion dependence.*
1033-5151	*RAEB***	*CR. Pancytopenic, not transfusion dependent on study entry. Bone marrow blasts decreased from 1%-2% to <0.5%. CBC normalized.*

** Diagnosed as AML by hematopathology consultant, Dr. JM Bennett.*
*** Consistent with RA not RAEB in this reviewer's opinion.*

Reviewer's Summary: Nine patients were transfusion-dependent at baseline and became transfusion independent with normalization of blood counts during the response. Six patients were not transfusion dependent at baseline, although some were pancytopenic. Patients with elevated bone marrow blast counts had normalization of blast count percentages during the

response. In the patient with CMML, pancytopenia and increased monocytes and granulocyte precursors in the blood were corrected during the response. The above data are consistent with CR or PR as stated by the sponsor.

Sub-group Analyses. Sponsor's Table 23 shows responses among patients within IPSS and FAB classifications, gender, age groups, prior MDS therapy and type of MDS.

Table 23 Subgroup Analyses of Overall Response Rate

Subgroup	Adjudicated Overall Response Rate (CR+PR)		
	Dacogen (N = 89) n/n (%)	Supportive Care (N = 81) n/n (%)	p-value*
IPSS Classification**			
Int-1	4/28 (14)	0/24 (0)	0.114
Int-2	8/38 (21)	0/36 (0)	0.005
High Risk	3/23 (13)	0/21 (0)	0.234
Gender			
Male	7/59 (12)	0/57 (0)	0.012
Female	8/30 (27)	0/24 (0)	0.006
Age			
< 65	6/23 (26)	0/30 (0)	0.004
65–74	7/42 (17)	0/35 (0)	0.014
≥ 75	2/24 (8)	0/16 (0)	0.507
FAB Classification**			
RA	3/12 (25)	0/12 (0)	0.217
RARS	0/7 (0)	0/4 (0)	–
RAEB	9/47 (20)	0/43 (0)	0.002
RAEB-t	2/17 (12)	0/14 (0)	0.488
CMML	1/6 (17)	0/8 (0)	0.428
Prior MDS Therapy			
Yes	3/27 (11)	0/19 (0)	0.256
No	12/62 (19)	0/62 (0)	< 0.001
Type of MDS			
De Novo	13/77 (17)	0/70 (0)	< 0.001
Secondary	2/12 (16)	0/11 (0)	0.478

* p-values are shown for information only.
** Original FAB and IPSS Classification from the Investigator Assessment.

Reviewer's Comments: The above subgroup analyses are handicapped by the small numbers of patients in each category. The following may be noted:

- *There appears to be a higher response in INT-2 group than in the other groups.*
- *The twice as high response rate among females is impressive, but is not confirmed in one of the Phase II trials.*
- *There appears to be a very low response rate among ≥ 75 year olds.*
- *There are no responses among RARS patients, but there are only 7 of them.*
- *Prior MDS therapy appears to result in a lower response rate.*
- *De novo and secondary MDS appear to have similar response rates.*

Among the 9 patients retrospectively adjudicated by Dr. Bennett to have had AML at baseline, there were 2 patients with CR, 1 patient with CRi (CR with incomplete blood count recovery), and 2 patients with PR for an ORR of 56% (5/9 patients) according to IWG AML Response Criteria , as shown in sponsor's Table 12. According to IWG MDS Response Criteria, there were

2 patients with CR and one patient with PR for an ORR of 33% (3/9 patients) (Appendix 16.2.6.25).

Table 12 Responses in Patients with AML at Baseline by AML IWG Criteria[2,3]

Response	Dacogen Arm N = 9 (%)	Supportive Care Arm N = 3 (%)
CR	2 (22%)	0 (0%)
CRi*	1 (11%)	0 (0%)
PR	2 (22%)	0 (0%)

Co-Primary Efficacy Endpoint: Time to AML or Death

The other co-primary efficacy endpoint was Time to AML or Death. The date of progression to AML was taken from either the Adjudication Reviewer's or Investigator data sets, whichever provided the earliest diagnosis of AML. The sponsor considered this approach to be the most conservative for defining the date of progression to AML.

The results for the ITT population at 92 events are shown in sponsor's Table 13. According to the co-primary endpoint model in the statistical analysis protocol, $p \leq 0.024$ was required statistical significance. A median time to event was 121 days greater in the DAC group than in supportive arm group. However, this difference had only a p=0.043 by two-sided Wilcoxon test for homogeneity of survival distributions and a p=0.160 by two-sided log-rank test.

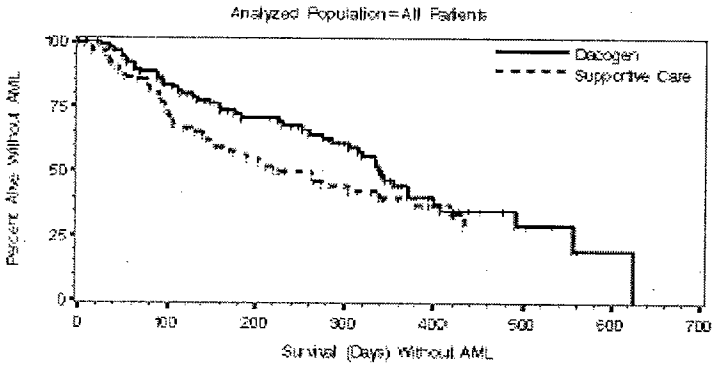
Sponsor's Table 13. Time to AML or Death* (ITT Population) at 92 Events

Parameter	Decitabine, N=89	Supportive, N=81	p-value
Number events (%)	46 (52%)	46 (57%)	
Median time to event, days (95% CI)	340 (285-407)	219 (148-379)	0.043, 0.160
Range, days (min – max)	24 – 624	7 - 432	

*Reflects analysis after 92 events. Patients who crossed over or never received randomized treatment are censored.

Sponsor's Figure 5 shows the Kaplan-Meier curves for this endpoint in the ITT population. There is an early separation between the curves, with the DAC curve showing delayed events. Subsequently, the DAC curve goes to zero because it reflects an actual event, while the supportive care group is truncated because the largest value is censored.

Figure 5 Time to AML or Death—All Patients



Subgroup Analyses. Exploratory subgroup analyses were performed using the Time to AML or Death for the IPSS groups, FAB classification, gender, age, type of MDS and prior MDS treatment. The data of these analyses are shown in the subsequent tables (all from sponsor's Table 24).

Reviewer's Table. Subgroup Analysis of Time to AML or Death by IPSS Classification

Population	Dacogen	Supportive Care	p-value[3]
IPSS Classification—Intermediate-1 (n)	**N = 28**	**N = 24**	
Number of events (%) Median (95% CI) days Range days	12 (43) 370 (225, NC) 24–400	9 (38) 417 (339, NC) 30–417	0.631[1], 0.507[2]
IPSS Classification—Intermediate-2 (n)	**N = 38**	**N = 36**	
Number of events (%) Median (95% CI) days Range days	18 (47) 371 (304–624) 48–624	20 (56) 263 (175–432) 45–432	0.094[1], 0.184[2]
IPSS Classification—High Risk (n)	**N = 23**	**N = 21**	
Number of events (%) Median (95% CI) days Range days	16 (70) 260 (115–338) 34–556	17 (81) 79 (39–169) 7–379	0.003[1], 0.010[2]
IPSS Classification—Intermediate-2 and High-Risk combined (n)	**N = 61**	**N = 57**	
Number of events (%) Median (95% CI) days Range days	34 (56) 335 (260–407) 34–624	37 (65) 189 (106-265) 7-432	0.005[1], 0.028[2]

The median duration of Time to AML or Death is markedly different in the High Risk category patients treated with DAC (260 days) as compared to those treated with supportive care (79 days). This difference was statistically significant, with unadjusted p-values of 0.003 (by two-sided Wilcoxon test) and 0.010 (by two-sided log-rank test). INT-2 category patients had a longer median duration when treated with DAC (371 days) than when treated by supportive care (263 days), but this difference was not statistically significant.

In contrast to High Risk and INT-2 groups of patients, there was little difference in Time to AML or Death between DAC arm patients and supportive care patients in INT-1 category. In this category of patients the median Time to AML or Death is shorter in the DAC group than in the supportive group by 47 days. This difference is not significant, however, it stands in contrast to longer median time in INT-2 and High Risk groups.

Kaplan-Meier plots of Time to AML or Death for INT-2 + High Risk Patients and High Risk Patients alone are shown in sponsor's Figures 6 and 7.

Figure 6 **Time to AML or Death—Intermediate-2 and High Risk Patients**

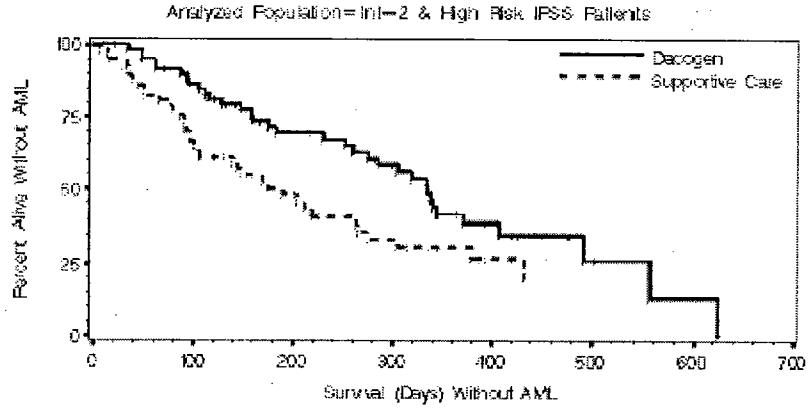
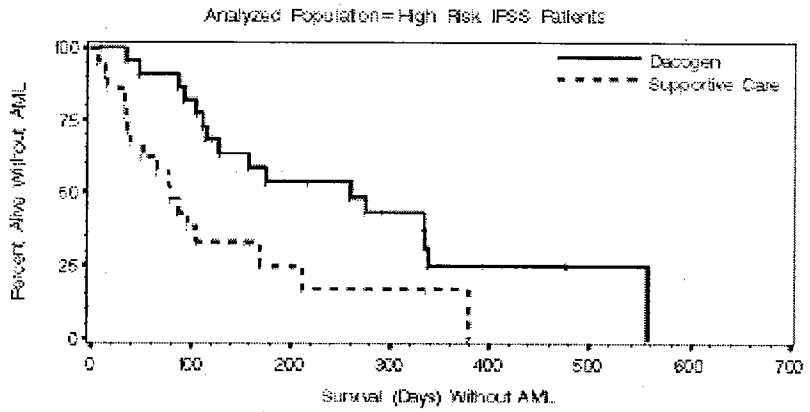


Figure 7 **Time to AML or Death—High Risk IPSS Patients**



Reviewer's Note: These data lead to the conclusion that, according to the Time to AML or Death endpoint, DAC shows the greatest efficacy in the High Risk patients, some efficacy in INT-2 patients, and none in INT-1 patients

Reviewer's Table. Subgroup Analysis of Time to AML or Death by FAB Classification (from sponsor's Table 24)

FAB Classification—RA (n)	N = 12	N = 12	
Number of events (%)	3 (25)	3 (25)	
Median (95% CI) days	624 (NC)	(NC)	0.900[1], 0.766[2]
Range days	24–624	92–100	
FAB Classification—RARS (n)	**N = 7**	**N = 4**	
Number of events (%)	4 (57)	4 (100)	
Median (95% CI) days	133 (52, NC)	118 (33–143)	0.443[1], 0.279[2]
Range days	39–133	33–143	
FAB Classification—RAEB (n)	**N = 47**	**N = 43**	
Number of events (%)	24 (51)	20 (47)	
Median (95% CI) days	338 (252–371)	274 (219, NC)	0.442[1], 0.657[2]
Range days	48–491	34–417	
FAB Classification—RAEB-t (n)	**N = 17**	**N = 14**	
Number of events (%)	10 (59)	13 (93)	
Median (95% CI) days	275 (128–556)	83 (50–189)	0.013[1], 0.011[2]
Range days	34–556	7–379	
FAB Classification—CMML (n)	**N = 6**	**N = 8**	
Number of events (%)	5 (83)	6 (75)	
Median (95% CI) days	319 (285–400)	136 (36–432)	0.248[1], 0.904[2]
Range days	285–400	30–432	

*NC means not calculable.

Reviewer's Notes: Analysis by FAB subgroups in general suffers from small numbers of patients. Patients with RA had the best prognosis, as could be expected. Patients with RAEB-T had the worst prognosis, and in this group decitabine appeared to demonstrate efficacy in prolonging the median Time to AML or Death. The median time in the DAC group was 275 days and in the supportive care group was 83 days. The difference was significant with unadjusted p-values of 0.013 and 0.011 by the two statistical methods.

Reviewer's Table. Subgroup Analysis of Time to AML or Death by Gender (sponsor's Table 24)

Population	Dacogen	Supportive Care	p-value*
Gender—Males (n)	**N = 59**	**N = 57**	
Number of events (%) Median (95% CI) days Range days	29 (49) 335 (252–556) 34–556	28 (49) 339 (175, NC) 14–432	0.476[1], 0.792[2]
Gender—Females (n)	**N = 30**	**N = 24**	
Number of events (%) Median (95% CI) days Range days	17 (57) 344 (285–491) 24–624	18 (75) 138 (78–274) 7–379	0.007[1], 0.015[2]

Reviewer's Note: Analysis by gender suggests that decitabine treatment was beneficial in females and not in males. Among females the median number of days to AML or Death was 344 days in the decitabine group and 138 days in the supportive care group (p-values of 0.007 and 0.015 by Wilcoxon and log-rank tests, respectively). Among males, the median times in both groups were the same.

Reviewer's Table. Subgroup Analysis of Time to AML or Death by Age Groups (sponsor's Table 24)

< 65 Years of Age (n)	N = 23	N = 30	
Number of events (%) Median (95% CI) days Range days	11 (48) 370 (260–491) 39–491	15 (50) 266 (118, NC) 51–417	0.530[1], 0.697[2]
65–74 Years of Age (n)	**N = 42**	**N = 35**	
Number of events (%) Median (95% CI) days Range days	20 (48) 334 (230, NC) 48–371	19 (54) 304 (130, NC) 7–432	0.260[1], 0.426[2]
75 or More Years of Age (n)	**N = 24**	**N = 16**	
Number of events (%) Median (95% CI) days Range days	15 (63) 335 (252–400) 24–624	12 (75) 143 (39–274) 14–379	0.031[1], 0.021[2]

***Reviewer's Note**: Analysis by age group suggests that decitabine treatment was beneficial only in patients 75 or more years of age in Time to AML or Death. The difference in the median Time to AML or Death was almost 200 days between the decitabine group and the supportive care group and this difference was significant with unadjusted p-values of 0.031and 0.021 by Wilcoxon and log-rank tests, respectively. Patients below 65 years of age had a median Time to AML or Death that was about 105 days longer in the decitabine group than in the supportive care group, but this difference was not statistically significant. Patients between 65 and 74 years of age had about the same median time to this endpoint in both groups.*

Reviewer's Table. Subgroup Analysis of Time to AML or Death by Prior MDS Therapy and by Type of MDS (from sponsor's Table 24)

Prior MDS Therapy—Yes (n)	**N = 27**	**N = 19**	
Number of events (%)	16 (59)	9 (47)	
Median (95% CI) days	314 (183–370)	417 (211, NC)	0.477[1], 0.387[2]
Range days	24–624	15–417	
Prior MDS Therapy—No (n)	**N = 62**	**N = 62**	
Number of events (%)	30 (48)	37 (60)	
Median (95% CI) days	354 (285–491)	189 (130–274)	0.008[1], 0.039[2]
Range days	34–556	7–432	
Type of MDS—de novo (n)	**N = 77**	**N = 70**	
Number of events (%)	36 (47)	40 (57)	
Median (95% CI) days	354 (319–556)	263 (154–379)	0.018[1], 0.044[2]
Range days	24–624	7–432	
Type of MDS—Secondary (n)	**N = 12**	**N = 11**	
Number of events (%)	10 (83)	6 (55)	
Median (95% CI) days	147 (111–334)	204 (79, NC)	0.973[1], 0.354[2]
Range days	34–370	33–204	

Reviewer's Notes: *DAC appeared to benefit patients without prior MDS therapy and not to benefit patients who had prior MDS therapy. In patients with no prior MDS therapy,* the *median time to AML or Death was about 163 days longer in the DAC group than in supportive care group. This difference was statistically significant with unadjusted p-values of 0.008 and 0.039 by Wilcoxon and by log-rank tests, respectively. In patients with prior MDS therapy, the median Time to AML or Death was 103 days shorter in the DAC group than in the supportive care group.*

DAC also appeared to benefit patients with de novo MDS and not to benefit patients with secondary MDS. Among patients with de novo MDS, the median time to AML or Death was about 91 days longer in the decitabine group than in the supportive care group. This difference was significant with unadjusted p-values of 0.018 by Wilcoxon test and 0.044 by log-rank test.

DAC appeared not to benefit patients with secondary MDS, although this conclusion is confounded by the small numbers of these patients (12 in the decitabine group and 11 in the supportive care group). Nevertheless, there were 10 events in the DAC group (83% of patients) and only 6 events in the supportive care group (55% of patients). Furthermore, the median Time to AML or Death was shorter by 57 days (a non-significant difference) in the DAC group.

Overall conclusion is still that small numbers of patients preclude any definite conclusion.

Analysis of Secondary Efficacy Endpoints

Secondary Endpoint: Survival. The median survival was not significantly different between the groups, as shown in sponsor's Table 15.

Table 15 Summary of Survival Analysis (ITT)—All Events

Population	Dacogen	Supportive Care	p-value[‡]
Intention to Treat Analysis	**N = 89**	**N = 81**	
Number of events* (%)	64 (72%)	55 (68%)	
Median (95% CI) days	391 (314–491)	417 (333–534)	0.750[1], 0.636[2]
Range days (min-max)†	24–745	30–797	

* Number of events reflects follow-up cut-off date of 30 August 2004. Patients crossing over or never receiving randomized treatment are censored.

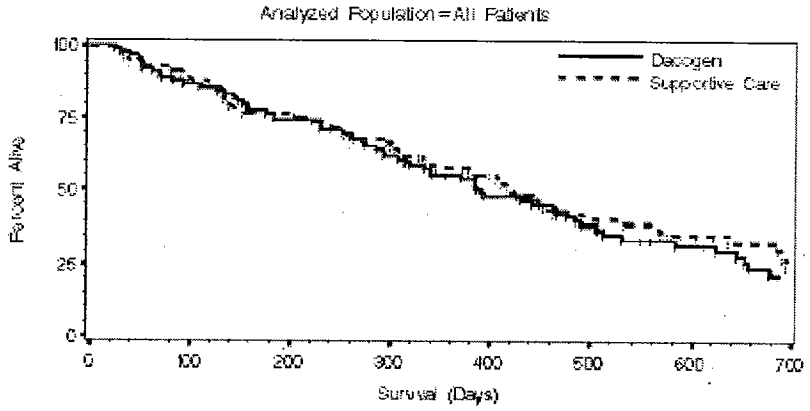
† From actual events only.

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

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

Survival analysis by a Kaplan-Meier plot is shown in sponsor's Figure 8.

Figure 8 Survival Analysis—All Patients



Secondary Endpoint: Transfusion Requirements.

Definitions:

- Responder (CR or PR): must be transfusion independent for a minimum of 8 weeks in absence of growth factors during the period of response.
- Transfusion Independent/Dependent: Pre-study – no transfusions for 8 weeks before randomization; during study – no transfusions during at least one 6 week period. Patients who did not meet these criteria were considered transfusion dependent.

RBC transfusion dependence in the study population: 70% (62/89) of patients randomized to DAC and 60% (49/81) of supportive care patients were RBC transfusion dependent during 8

weeks prior to randomization. In the DAC arm, 24/62 patients became transfusion independent, while 38 continued to be transfusion dependent. In the Supportive Care arm, 13 patients of 49 became transfusion independent, while 36 remained dependent. These data are shown in Sponsor's Table 18.

Table 18 RBC Transfusion Status—All Patients

Pre-Study vs. On Study	Dacogen N = 89 (%)	Supportive Care N = 81 (%)
Dependent at Baseline	**N = 62 (70)**	**N = 49 (60)**
Dependent to Independent	24 (39)	13 (27)
Remaining Dependent	38 (61)	36 (73)
Independent at Baseline	**N = 27 (30)**	**N = 32 (40)**
Remaining Independent	23 (85)	24 (75)
Independent to Dependent	4 (15)	8 (25)

Source: Table 14.2.4.3 RBC Transfusion Status—All Patients

Platelet transfusion dependence in the study population: Twenty of 89 patients randomized to DAC were platelet transfusion dependent at baseline; 12 became transfusion independent, 9 remained dependent. Eleven of 69 transfusion independent patients became dependent during the study. Seventeen of 81 patients randomized to supportive care were dependent at baseline and 11 of them became transfusion independent, 6 remaining dependent. Seven of 64 patients who were independent at baseline became dependent during the study. These findings are summarized in Sponsor's Table 19.

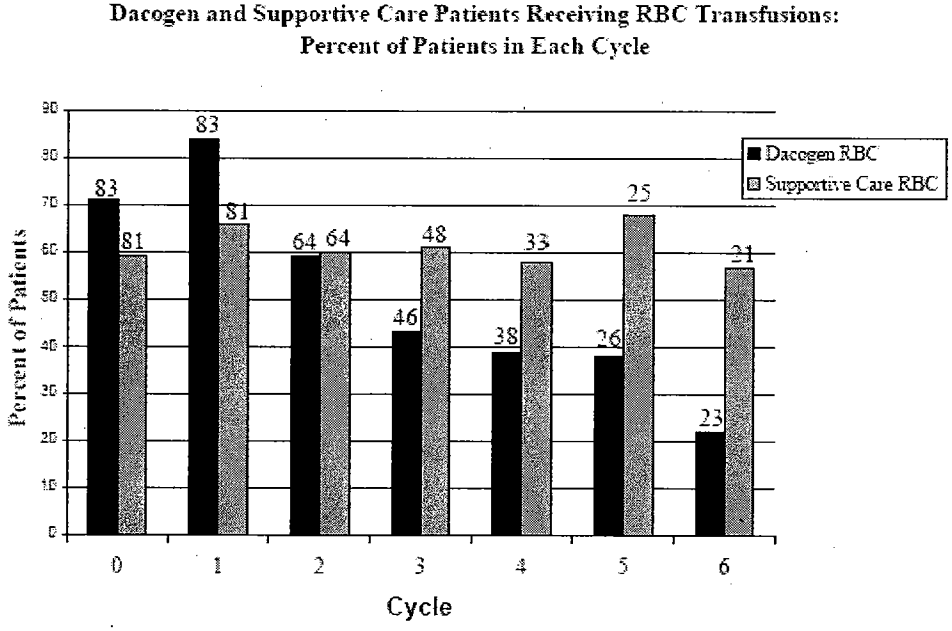
Table 19 Platelet Transfusion Status—All Patients

Pre-Study vs. On Study	Dacogen N = 89 (%)	Supportive Care N = 81 (%)
Dependent at Baseline	**N = 20 (24)**	**N = 17 (21)**
Dependent to Independent	12 (57)	11 (65)
Remaining Dependent	9 (43)	6 (35)
Independent at Baseline	**N = 69 (76)**	**N = 64 (79)**
Remaining Independent	58 (84)	57 (89)
Independent to Dependent	11 (16)	7 (11)

Source: Table 14.2.4.4 Platelet Transfusion Status—All Patients

Frequency of RBC Transfusions by Cycle – All Patients: Sponsor's bar graph (Figure 9) demonstrates that the percentage of patients receiving RBC transfusions remained about the same (about 60%) during 6 cycles in the supportive care group, while in the DAC-treated group it decreased from about 70% to about 20%. *Reviewer's comment: These data are difficult to interpret as >70% patients in both arms left the study by cycle 6.*

Figure 9 **RBC Transfusion Requirements by Cycle—Dacogen vs. Supportive Care Patients**



Source: Table 14.2.4.5 RBC Transfusion Requirements by Cycle—Dacogen vs. Supportive Care Patients
Source: Table 14.2.4.5.1 Patients Receiving Transfusions—Dacogen vs. Supportive Care Patients

Transfusion status in responders: Of the 15 responders, 9 were RBC transfusion dependent and 4 of them were also platelet transfusion dependent. All transfusion dependent patients became transfusion independent during the period of response. Six responders were RBC transfusion independent at baseline and remained independent. Eleven patients were platelet transfusion independent at baseline and remained independent. These data are summarized in Reviewer's Table below (from Sponsor's Table 16).

Reviewer's Table. Transfusion Status Changes in Decitabine Responders (CR + PR)

Transfusion Status	RBC	Platelets
Dependent at Baseline • Dependent to Independent	N=9 9 (100%)	N=4 4 (100%)
Independent at Baseline • Remained Independent	N=6 6 (100%)	N=11 11 (100%)

Hematologic Improvement in patients: Hematologic Improvement is a secondary endpoint, but does not relate to the primary efficacy endpoint. These data will be summarized in text only. In the DAC arm, six patients who were RBC transfusion dependent at baseline became independent (HI-E Major response); two patients who were platelet transfusion dependent prior to study became independent (HI-P Major response); and one patient who was RBC and platelet transfusion dependent before study became transfusion independent during the response (HI-E Major and HI-P Major response). In the Supportive Care arm 2 patients had HI-P Major as best response, both being platelet transfusion independent throughout the study.

Frequency of RBC and Platelet Transfusions: Comparison of all DAC arm patients with Supportive care patients is shown in Reviewer's Table below (from Sponsor's Table 17). In the DAC arm patient group, RBC transfusion frequency decreased by about 26% and platelet transfusion frequency increased. In the supportive care group, RBC transfusion frequency remained stable, while platelet transfusion frequency increased.

Reviewer's Table. Frequency of RBC and Platelet Transfusions, DAC Arm Patients vs. Supportive Care Patients

	Period	All DAC, N=89	Supportive Care, N=81
RBC transfusions per patient (mean)	Pre-study (8 weeks)	2.3	1.4
	On-study (6-week cycles)	1.7	1.5
Platelet transfusions per patient (mean)	Pre-study (8 weeks)	0.8	0.6
	On-study (6-week cycles)	1.1	0.9

A responder analysis demonstrates that RBC and platelet transfusions per patient (means) decreased in DAC responders, and did not decrease in DAC non-responders or in supportive care patients.

Reviewer's Table. Average Number of RBC and Platelet Transfusions per Interval or Cycle

	Period	DAC Responder N=15	DAC Non-Responder, N=74	Supportive Care N=81
RBC transfusions per patient (mean)	Pre-study (8 weeks)	1.7	2.4	1.4
	On-study (6-week cycles)	0.5	2.1	1.5
Platelet transfusions per Patient (mean)	Pre-study (8 weeks)	0.9	0.7	0.6
	On-study (6-week cycles)	0.3	1.4	0.9

Secondary endpoint: Rate of Febrile Neutropenia. The incidence of febrile neutropenia was higher in DAC treatment group than in supportive care group. It occurred in 24 (29%) of DAC arm patients and 5 (6%) of supportive care patients. The difference was significant (unadjusted $p < 0.001$).

Secondary endpoint: Rate and Duration of Improvement (CR + PR + HI). These data are shown in Sponsor's Table 20. As noted above in the primary efficacy endpoint, there were 17% of patients with CR + PR in the DAC group and none in supportive care group. There were 12% of patients in the DAC group with HI, and 6% in supportive care. The Overall Improvement Rate (CR + PR + HI) was 29% in the DAC group and 6% in the supportive care group, a highly significant difference. Median days to response were about one-half in the DAC group than in the supportive care group. Median duration was about the same in both groups.

Median Duration of CR was 288 days (range, 182 to 346 days), and median duration of PR was 239 days (range, 131 to 342 days) (data from Appendix 16.2.6.2).

Reviewer's Notes:

- *Durations of CR and PR are underestimates, since 12/15 responders were discharged from the study because they completed treatment, not because they were no longer in response status. The remaining three patients remained transfusion independent, but one CR patient had not recovered normal blood counts at the time of discontinuation, one CR patient was discontinued from the study because of a non-treatment-related adverse event (M. avium mediastinal adenopathy), and one PR patient changed to another drug for MDS after two cycles, while still in PR. These data are in Appendices 16.2.1.1, 16.2.6.2, and 16.2.6.27.*

Five HI patients were discontinued early (within 2 cycles) from the study, two because they died, one decided not to continue treatment, one was non-compliant, and one received other therapy.

Secondary endpoint: Quality of Life Analysis. EORTC Scale Version 3.0 was used to assess quality of life at baseline, at the end of each treatment cycle and at the end of study. DAC arm patients had the following statistically superior QoL parameters than supportive care arm patients:

- Global health status
- Dyspnea
- Fatigue

There were no parameters in which supportive arm patients had QoL parameters that were superior to those in DAC arm patients.

Secondary endpoint: Cytogenetic evaluations. Cytogenetic evaluations were available for 84 DAC patients and 77 supportive care patients; 46/84 (55%) DAC patients and 48/77 (62%) supportive care patients had clonal abnormalities at baseline. At baseline, the cytogenetic IPSS prognostic classes were equally represented in the two treatment arms (Sponsor's Table 7 Baseline Demographics, above). On follow-up, 48/49 (98%) DAC patients and 33/46 (72%) supportive care patients had cytogenetic results assessed by MDS IWG criteria.

As shown in sponsor's Table 21, 9/48 (19%) of DAC patients had a major cytogenetic response and 1/48 had a minor response. Among supportive care patients 2/33 (6%) had a major cytogenetic response. Among patients with CR + PR in the DAC arm, 8/15 had a major cytogenetic response. Of the 2 patients with cytogenetic response in the supportive care arm, one had a HI, the other progressive disease.

Table 21 Cytogenetic Responders

Patient No.	IPSS Classification	Cytogenetic Response (start date)	Best Clinical Response
Dacogen Patients			
0121-5011	Intermediate (chromosome +8)	Major (2/5/02)	CR (PR 2/5/02)
0121-5065	Poor (complex, chromosome -7)	Major (9/30/02)	CR (PR 9/3/02)
0143-5036	Poor (complex, chromosome -7)	Major (5/28/02)	CR (PR 5/28/02)
1002-5123	Intermediate (chromosome +8)	Major (2/27/03)	CR (PR 2/27/03)
1032-5067	Intermediate (-10q)	Major (2/18/03)	CR (8/21/02)
1033-5151	Poor (chromosome -7)	Major (6/25/03)	CR (4/24/03)
1008-5060	Intermediate (chromosome +8)	Major (12/23/02)	PR (9/20/02)
1008-5134	Poor (complex)	Minor (4/2/03)	PR (2/12/03)
1006-5045	Good (-20q)	Major (7/9/02)	HI (5/17/02)
Supportive Care Patients			
1006-5020	Good (-Y)	Major (9/30/02)	HI (5/8/02)
1007-5039	Intermediate (chromosome +21)	(Major at two months (4/25/02) transiently; worsened at end of study: +21, + 8, +9, + 14, +15; 8/27/02)	PD (5/30/02)
Supportive Care Patient Crossed Over to Dacogen			
1046-5078	Good (del 5q)	Major three months after crossing over to Dacogen; (12/3/02)	PD (8/2/02 on SC) CR (3/12/03 on Dacogen)

Source: Table 14.2.8.1 Summary of Cytogenetic Responses – Best Response; Appendix 16.2.4.2 Listing of Cytogenetics at Baseline

Reviewer's Notes:

- *In the DAC arm, 7/8 CR patients had a major cytogenetic response, and 2/7 PR patients had a cytogenetic response (one major, one minor). Thus, there appears to be a correlation between a major cytogenetic response and CR.*
- *On the other hand, the predictive power of the IPSS classification by cytogenetics was poor. Of the 7 CR patients only 1 had "good" classification (del 5q), 3 had "intermediate", and 3 had "poor". Of the 2 PR patients, one had "intermediate" and one had "poor." In the supportive care arm, one patient with a "good" classification had a HI, and one with "intermediate", progressive disease. Reviewer's Table (data from*

Sponsor's Tables 7 and 21) shows this poor correlation between the IPSS Cytogenetic Prognostic Group and response to DAC. Of the 9 patients with CR or PR, who were classified by IPSS Cytogenetic Prognostic Groups, 4 were in "intermediate" and 4 in "poor" groups; only one was in the "good" group.

Reviewer's Table. Lack of Correlation between IPSS Cytogenetic Prognostic Group and Response to Treatment with Decitabine

IPSS Cytogenetic Prognostic Group at Baseline	Decitabine arm, N=89	CR + PR N=15	No response N=74
Good	44	1	43/44 (98%)
Intermediate	14	4	10/14 (71%)
Poor	26	4	22/26 (85%)
Not evaluable	5		

Important clinical outcomes for patients with CR or PR. The sponsor presented an analysis between responders and non-responders of the primary clinical endpoint Time to AML or Death and a secondary endpoint, survival time. The non-responder group (n=155) included both DAC-treated and supportive care patients. An analysis of responders vs. non-responders in the DAC treatment arm was not presented. Sponsor's data on all patients are shown in sponsor's Table 22.

Table 22 Clinical Outcomes for Responders vs. Non-Responders

Clinical Endpoint	Responders N = 15	Non-Responders N = 155	p-values†
Primary Clinical Endpoint			
Time to AML or Death			
No. of Events	4 (27%)	88 (57%)	0.002[1]
Median days (95% CI)	491 (400–491)	274 (204–339)	0.010[2]
Range: min-max	334–491	7–624	
Secondary Clinical Endpoints			
Survival Time			
No. of Events	7 (47%)	112 (72%)	0.029[1]
Median days (95% CI)	657 (485, NC)	384 (314–448)	0.007[2]
Range: min-max	272–678	24–797	

† P-values are provided for informational purposes only NC = Not Calculable

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

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

Source: Table 14.2.2.3 Times to AML or Death for—Responders vs. Non-responders; Table 14.2.3.2 Summary of Survival Analysis—Responders vs. Non-Responders; Appendix 16.2.6.21 Listing of Times to AML or Death—Patient Data; Appendix 16.2.6.23 Listing of Patient Survival Analysis Data

The sponsor's conclusion is that CR + PR patients had a median of 217 additional days until Progression to AML or Death, and a median of 273 additional days of survival as compared to non-responders. In addition, responders were RBC and platelet transfusion independent during the period of response, as described above.

Statistical and Analytical Issues

- Two co-primary endpoints, Overall Response Rate (CR + PR) to randomized treatment and Time to AML or Death. A two-sided $p \geq 0.024$ indicates that the difference is statistically significant.
- Adjustment for covariates. Analyses of primary and secondary endpoints tested the primary effect of treatment group without adjusting for covariates. Sub-group analyses are presented below.
- Handling of Dropouts and Missing Data. Lost to follow-up patients were censored on the date the patient was last known to be alive without AML. There are no missing values for the primary endpoint of Time to AML or Death. Missing values of secondary endpoints were mainly due to early patient withdrawal from the study. These were not estimated.
- Multicenter Studies. ANOVA analysis was carried out for possible interaction between center group and treatment. (Seven center groups were defined for the number of events (AML or death)). There was no interaction between center group and treatment (p=0.22) and in between centers within a group (p=0.39).

- Evaluable ("Efficacy") subset of patients were: 1) patients randomized to DAC who never received the drug and 2) patients randomized to DAC who did not receive 2 cycles of treatment.

Subgroup Analyses. Overall Response Rate data are summarized in Sponsor's Table 23 shown below.

Reviewer's Notes:

- *The size of the study and the numbers in each subset category limit the confidence in these subset analyses. The results can only be treated as preliminary and suggestive in most cases. Thus,*
  - *Response rates appear to be similar in the 3 IPSS classifications,*
  - *Both females and males respond, but the twice as high response in females would need to be confirmed,*
  - *The response rate appears to be the highest in younger patients and decreases with age, but these data would need to be confirmed,*
  - *The response occurred in patients with 4 subtypes of MDS (not RARS), but it is uncertain that response depended on the subtype (i.e. highest in RA and RAEB),*
  - *Prior MDS therapy was probably not a factor in response, and*
  - *The response rates were the same in de novo and in secondary MDS (but there were only 2 responders in only 12 patients in the latter category).*

Table 23 Subgroup Analyses of Overall Response Rate

Subgroup	Adjudicated Overall Response Rate (CR+PR)		
	Dacogen (N = 89) n/n (%)	Supportive Care (N = 81) n/n (%)	p-value*
IPSS Classification**			
Int-1	4/28 (14)	0/24 (0)	0.114
Int-2	8/38 (21)	0/36 (0)	0.005
High Risk	3/23 (13)	0/21 (0)	0.234
Gender			
Male	7/59 (12)	0/57 (0)	0.012
Female	8/30 (27)	0/24 (0)	0.006
Age			
< 65	6/23 (26)	0/30 (0)	0.004
65–74	7/42 (17)	0/35 (0)	0.014
≥ 75	2/24 (8)	0/16 (0)	0.507
FAB Classification**			
RA	3/12 (25)	0/12 (0)	0.217
RARS	0/7 (0)	0/4 (0)	–
RAEB	9/47 (20)	0/43 (0)	0.002
RAEB-t	2/17 (12)	0/14 (0)	0.488
CMML	1/6 (17)	0/8 (0)	0.428
Prior MDS Therapy			
Yes	3/27 (11)	0/19 (0)	0.256
No	12/62 (19)	0/62 (0)	< 0.001
Type of MDS			
De Novo	13/77 (17)	0/70 (0)	< 0.001
Secondary	2/12 (16)	0/11 (0)	0.478

* p-values are shown for information only.

Subgroup Analysis of Time to AML or Death. Sponsor's Table 24 will be condensed to show in each subgroup number of patients, number of events, and median time in days. CIs, range of days, percentages of patients affected, and p values will be omitted.

Reviewer's Table. Subgroup Analyses of Time to AML or Death

Population	Decitabine arm median (days)	Supportive care median (days)
IPSS Classification		
Int-1	370	417
Int-2	371	263
High risk	260	79
Int-2 + High risk	335	189
Gender		
Females	344	138
Males	335	339
Age (years)		
<65	370	265
65-74	334	304
≥75	335	143

FAB Classification		
RA	624	Not calculable
RARS	133	118
RAEB	338	274
RAEB-t	275	83
CMML	319	136
Prior MDS Therapy		
Yes	314	417
No	354	189
Type of MDS		
De novo	354	263
Secondary	147	204

Reviewer's Notes:

- *As noted above, each group is not large, and the number of events in each group ranges from about 40% to 80% to 90% (as in RAEB-t and CMML). Therefore, any conclusions can be regarded only as tentative.*
- *There is a highly significant difference in median time to event in IPSS High Risk patients (unadjusted p-values of 0.003 and 0.010 by Wilcoxon and log-rank tests, respectively). There were about 23 patients in DAC arm and 21 patients in supportive care arm, of whom about 16 (DAC arm) and 17 (supportive care arm) had an event. The differences in median survival between the DAC arm and the supportive care arm in INT-2 patients and INT-1 patients were not significant.*
- *The median survival in females was significantly shorter in the supportive care arm than in DAC arm (unadjusted p values of 0.007 and 0.015 by the two methods). In males the median survival was the same in both arms and equal to that of females in the DAC arm.*
- *The median survival in patients ≥ 75 years was significantly shorter in the supportive care arm than in the DAC arm. Median survivals were about the same in all age groups in the DAC arm and in < 65 – 74 year olds in the supportive care arm.*
- *Median survivals decreased in the FAB subtypes in the DAC arm in the following order: RA>RAEB>CMML>RAEB-t>RARS. Median survivals were significantly shorter in the supportive arm RAEB-t patients (unadjusted p values 0.013 and 0.011). They were also shorter in CMML patients, but the number of patients (6 and 8) and events (5 and 6) were too few to ascertain significance. Median survivals were about the same in both arms in RAEB and RARS patients.*
- *Median survival in patients who had no prior therapy for MDS was significantly longerin the DAC arm than in the supportive care arm (unadjusted p values of 0.008 and 0.039). There was no difference between arms in patients with prior therapy for MDS.*
- *De novo MDS patients in the supportive care arm had significantly shorter median survival than these patients had in the DAC arm (unadjusted p values of 0.018 and 0.044).*

Sponsor's Efficacy Conclusions for D-0007 Clinical Study

- Efficacy of DAC was demonstrated by an Overall Response Rate (CR + PR) of 17% (15/89) vs. 0% in Supportive Care ($p<0.001$). There were 8 CRs and 7 PRs.

- The median time to response onset for DAC was 89 days.
- Responses to DAC were generally of long duration. The median duration of response was 266 days (131-346 days). DAC responders had a median of 217 additional days until Progression to AML or Death (491 vs. 274) as compared to non-responders. DAC responders had a median of 273 additional days of survival (657 vs. 384 days) compared to non-responders.
- DAC responders became RBC and platelet transfusion independent during response.
- Patients in the DAC arm had a median time to AML or Death of 340 days, compared to patients in the Supportive Care arm, who had a median time to AML of death of 219 days (the difference was significant by the Wilcoxon test (p=0.043); and not significant by the log-rank test (0.160)).
- An exploratory analysis (Cox proportional hazards model) showed that patients in the Supportive Care arm had 1.68-fold greater rate of progression to AML or Death than patients in the DAC arm.
- IPSS High Risk Patients had a longer survival as a result of DAC treatment (median survival of 260 days vs. 79 days in the supportive care patients). INT-1 and INT-2 patients did not have a significantly longer survival as compared to supportive care patients. (Median survival of INT-2 patients in the DAC arm was longer than in the supportive care arm, but the difference was not significantly different (p-values were 0.094 and 0.184 by Wilcoxon and log-rank methods, respectively)).
- DAC patients that were transfusion dependent became transfusion independent during CR or PR. Typically, they had increased transfusion requirement early on in treatment.
- DAC patients had significantly better Global Health Status, physical functioning, less fatigue and less dyspnea by QoL measures.

Supportive Phase II Studies PCH 95-11 and PCH 97-19

Regulatory: Study PCH 95-11 was initiated and completed by Pharmachemie B.V., Haarlem, The Netherlands (April 15, 1996 to June 16, 1998). Study PCH 97-19 was initiated by Pharmachemie and completed by SuperGen (October 8, 1997 to September 28, 2001). Supergen acquired U.S. rights to decitabine and transferred the U.S. IND on November 5, 1999.

Study design: Both studies were multi-center (7 centers in study 95-11, and 9 centers in study 97-19, all in The Netherlands, Belgium and Germany), open-label, single arm studies. Both studies enrolled MDS patients of all five FAB subtypes. Patients were classified by the IPSS classification retrospectively, as the IPSS classification was devised after the initiation of these studies. Both studies enrolled patients with either primary or secondary MDS. Study PCH 97-19, but not study 95-11, permitted enrollment of patients who had been previously treated with DAC and relapsed.
Both studies used a similar DAC dosage regimen as the Phase III study D-0007 (15 mg/m^2 infused IV over 4 hours every 8 hours for 3 consecutive days of a 6-week cycle; the only difference is the length of infusion, 4 hours instead of 3 hours in the D-0007 study). A minimum of two courses and a maximum of 6 courses could be administered, although a few patients

received eight. Patients who achieved CR, PR or stable disease (SD) after two courses received two additional courses. Patients who relapsed or progressed were taken off the study.

In both Phase II studies, the **primary endpoints** were

- Best hematological response,
- Duration of response, and
- Overall survival.

Hematological response criteria, which were the same in both Phase II studies are shown below.

- **Complete Remission (CR)**: The bone marrow was normocellular or slightly hypocellular, contained less than 5% blast cells (M1 marrow) along with a full normalization of the hemogram (Hb, granulocytes, and platelets within normal ranges).
- **Partial Remission (PR)**: A > 50% decrease in bone marrow myeloblasts and an increase in hemoglobin > 1.5 mmol/L, an increase in platelet count > 50 x 10^9/L and an increase in granulocyte count > 1 x 10^9/L.
- **Improvement**: Decreased infections, bleeding episodes, 50% decrease in transfusion requirement, decrease of dyspoiesis and improvement in peripheral blood counts but not enough to qualify for PR and CR.
- **Stable Disease (SD)**: Absence of CR, PR or improvement but without clear disease progression.
- **Relapse**: Patients with a CR who developed > 5% myeloblasts and/or deterioration of blood counts leading to (increased) transfusion requirements.
- **Progression**: Deterioration of blood counts leading to (increase) transfusion requirements or increase in myeloblast count of > 10%.

The **secondary endpoints** in both studies were:

- Transfusion requirements, and
- Changes in ECOG PS.

Reviewer's Notes:
1. Definitions of CR and of PR are different in the Phase III trial and in the two Phase II studies with respect to peripheral blood counts. In CR, CBC is normal in the Phase II studies and less than normal in the Phase III trial (Hgb >11 g/dL, ANC ≥ 1500/mm^3, platelets ≥ 100,000/mm^3). In PR, CBC is the same as in CR in Phase III trial and lower values in the Phase II studies, as above. More importantly, the response had to last for 2 cycles in the Phase III study; there was no such requirement for response duration in the Phase II trials. These changes are due to re-formulations of criteria by the IWG.
2. In PCH 95-11 the secondary efficacy variable is ECOG performance status. In PCH 97-19 the secondary efficacy variables are ECOG performance status, bone marrow examination for percentage of blasts, and differential leukocyte count for blast percentage. Transfusion requirements are not listed as an efficacy endpoint. Transfusion data are in the Safety sections of the protocols.

Patient demographics are shown in reviewer's table below (data from sponsor's Table 9 in Section 2.5)

Reviewer's Table. Demographics of Patients in Studies PCH 95-11 and PCH 97-19

Characteristic	PCH 95-11, N=66	PCH 97-19, N=98*
Age in years, mean (range)	68 (37-84)	70 (51-87)
<65	24 (36%)	22 (22%)
65-74	29 (44%)	48 (49%)
≥75	13 (20%)	28 (30%)
Gender		
Male	46 (70%)	72 (73%)
Female	20 (30%)	26 (27%)
FAB Classification		
RA	7 (11%)	9 (9%)
RARS	0	2 (2%)
RAEB	26 (39%)	34 (35%)
RAEB-t	24 (36%)	33 (34%)
CMML	8 (12%)	14 (14%)
AML	0	5 (5%)
Unknown	1 (2%)	1 (1%)
IPSS Classification		
Low	1 (2%)	6 (6%)
INT-1	19 (29%)	18 (18%)
INT-2	25 (38%)	14 (14%)
High	21 (32%)	37 (38%)
Unknown		23 (24%)

*Eleven patients were relapsed, 12 had been previously treated with DAC in other trials.

Disposition of Patients: In PCH 95-11 41% of patients completed the study. The reasons for not completing the study are listed in Reviewer's Table below (data from Table 3 in PCH 95-11 Study Report and Table 2 in PCH 97-19 Study Report).

Reviewer's Table. Reasons for Patient Discontinuations from Study

Reason	PCH 95-11, N=66	PCH 97-19, N=98
Completed study	27 (41%)	41 (42%)
Relapse/Progression	13 (20%)	18 (18%)
Death	11 (17%)	17 (17%)
Adverse Event	5 (8%)	3 (3%)
Withdrawal	4 (6%)	3 (3%)
Other	6 (9%)	16 (16%)

Evaluable Patients in the ITT Population: In PCH 95-11, 48/66 (73%) patients were classified as evaluable for response. In order to be considered evaluable, patients had to have received two cycles of DAC therapy and a cycle 2 assessment. Eighteen patients were not considered evaluable for the reasons shown in reviewer's table below. In PCH 97-19, 62/98 (62%) patients were classified as evaluable for response. Thirty-six patients were considered not evaluable for

reasons shown in reviewer's table below (data from Table 4 in PCH 95-11 Study Report and from Table 3 in PCH 97-19 Study Report).

Reviewer's Table. Reasons for Patients Being Not Evaluable in PCH 95-11

Reason	No. of patients, PCH 95-11
Adverse event – discontinued after one course	4
Early death – received only one course	4
Disease progression – received only one course	4
Withdrawal of consent	1
No recovery of thrombopoiesis after one course	1
Early death - No bone marrow at 6 weeks after course 2	2
Early death – died one week after start of course 2	1
Total	18

Reviewer's Table. Reasons for Patients Being Not Evaluable in PCH 97-19

Reason	No. of patients, PCH 97-19
Received only one course	25
Early death – received 2 courses	3
Received 2 or 3 courses, but no F/U bone marrow available	4
AML	1 (also 3 others above)
Received previous decitabine, but was not relapsed	1
Received previously other chemotherapy, not decitabine	2 (also one other above)
Total	36

Protocol violations: In PCH 95-11, seven patients did not fulfill all inclusion and exclusion criteria. One had only oral informed consent, five did not have normal renal, hepatic and cardiac function, one had prior treatment for MDS with a cytotoxic agent.

In PCH 97-19, seventeen patients did not fulfill inclusion and exclusion criteria. Five had only oral informed consent. Six did not have normal renal, hepatic and cardiac function. Five were diagnosed with AML not MDS. Three had received other chemotherapy. One was previously treated with decitabine, but was not in the first relapse.

Primary Efficacy Endpoint: Best hematological response, which was assessed by each investigator and also adjudicated by a Chairman's review. The table below (data from sponsor's Table 10, section 2.5) presents response rates according to the Chairman's review.

Reviewer's Table. Response to DAC Treatment in All Enrolled Patients in PCH 95-11 and PCH 97-19

Response	PCH 95-11, N=66	PCH 97-19, N=98
CR + PR	17 (26%)	24 (24%)
CR	14 (21%)	19 (19%)
PR	3 (5%)	5 (5%)
HI (<PR)	8 (12%)	16 (16%)

In addition to Overall Response Rate (CR + PR), which was consistent at 24% and 26% in the two studies, the study determined the rate of hematological improvement, a response that was less than a PR.

Since there were 18 patients that were considered non-evaluable in PCH 95-11, response rates for evaluable patients are shown below in Reviewer's Table (data from PCH 95-11 study report Table 9 and from PCH 97-19 study report Table 11).

Reviewer's Table. Response to DAC Treatment in Evaluable Patients in PCH 95-11 and PCH 97-19

Response	PCH 95-11, N=48	PCH 97-19, N=62
CR + PR	17 (35%)	23 (40%)
CR	14 (29%)	19 (33%)
PR	3 (6%)	4 (7%)
HI (<PR)	8 (17%)	13 (23%)

Reviewer's Notes:
The overall response rates were similar in the two Phase II studies to those in the Phase III study (the differences are probably due to differences in response criteria) and support the overall efficacy conclusion.
The sponsor presents the data in PCH 97-19 separately for patients who had not been previously treated with DAC and for patients who had been treated and relapsed. Among the 11 relapsed patients there were no CRs and 1 PR for an overall response rate of 9%. There were also 3 HIs. Clearly, the results were poorer than in previously untreated patients. The reviewer merged both populations into one, as this subset is too small to lead to a definitive conclusion.

Subgroup Analyses: Reviewer's Table below shows the analyses by gender, age, and MDS classifications.

Reviewer's Table. Subgroup Analyses of the Overall Response Rate (CR + PR)

Characteristic	PCH 95-11, N=66	PCH 97-19 (N=98)
Age (years)		
< 65	5/24 (21%)	4/22 (18%)
65-74	5/29 (17%)	11/48 (23%)
≥ 75	5/13 (38%)	9/28 (31%)
Gender		
Male	7/46 (15%)	18/72 (25%)
Female	8/20 (40%)	6/26 (23%)
FAB Classification		
RA	1/7 (14%)	2/9 (22%)
RARS	-	1/2 (50%)
RAEB	8/26 (31%)	10/34 (29%)
RAEB-t	5/24 (21%)	5/33 (15%)
CMML	2/8 (25%)	4/14 (29%)
IPSS Classification*		
Low	0/1	4/6 (67%)
INT-1	4/19 (21%)	4/18 (22%)
INT-2	6/25 (24%)	7/14 (50%)
High Risk	7/21 (33%)	9/37 (24%)

* Includes patients with IPSS classification data only.

Reviewer's Notes:
These subgroup analyses show some similarities and some differences with subgroup analyses in the Phase III trial:

- *In both Phase II trials patients 75 years or older did not have a lower response rate as in the Phase III trial,*
- *A higher response rate in females occurred in PCH 95-11, as in the Phase III trial, but not in PCH 97-19,*
- *Responses occurred at about the same frequency in all FAB subgroups in both Phase II trials as in the Phase III trial. However, there were only 9 RARS patients in all three trials with one responder in PCH 97-19,*
- *IPSS classification may not predict responses, which in all three trials occurred at similar frequencies in INT-1, INT-2, and High Risk groups. INT-2 patients may have the highest response rate.*

Primary Efficacy endpoint: Duration of Response. In PCH 95-11 the median duration of CR + PR was 250 days, and the mean duration was 263±21.3 (SD) days. In PCH 97-19 the median duration of CR + PR was 146 days, and the mean duration was 148±25 (SD) days.

Primary Efficacy endpoint: Survival. In PCH 95-11 the median survival was 401 days. In PCH 97-19 the median survival was 468 days.

Secondary Efficacy endpoints: 1) ECOG PS did not change over the course of either study, 2) percentages of blasts in peripheral blood and in bone marrow decreased in both studies.

6.1.4 Clinical Microbiology: see above under Clinical Microbiology.

6.1.5 Efficacy Conclusions ***(Please note 4.3 Data Quality and Integrity)***

1. The co-primary endpoints in the controlled Phase III trial were 1) Overall Response Rate (CR + PR) and 2) Time to Progression to AML or Death. The difference in Overall Response Rate (17%) in the DAC arm was significantly greater than in the supportive care arm (0%) ($p < 0.001$, Fisher's Exact test). The difference in Time to Progression to AML or Death between the DAC arm and supportive care arm did not reach statistical significance (p=0.160 by log-rank test, p=0.043 by Wilcoxon test). Thus, efficacy of DAC was demonstrated by the Overall Response Rate, but not by Time to Progression to AML or Death ($p \geq 0.024$ was required to establish statistical significance for either endpoint).
2. Responses to DAC occurred in the controlled study and in the two single-arm studies at similar rates. Reviewer's table below shows the data for the ITT populations in the three studies. The ORR for the three studies was 22%.

Reviewer's Table. Summary of Overall Response Rates to DAC in MDS (ITT Populations)

Response	D-0007 N=89	PHC 97-19 N=98	PHC 95-11 N=66	Total, N=253
Overall (CR + PR)	15 (17%)	24 (24%)	17 (26%)	56 (22%)
CR	8 (9%)	19 (19%)	14 (21%)	41 (16%)
PR	7 (5%)	5 (5%)	3 (5%)	15 (6%)

3. The overall response rates in the Evaluable populations were higher than in the ITT populations, as shown in the Reviewer's table below. The ORR for the three studies was 31%. These higher response rates are to be expected, as patients who failed to complete at least two cycles of therapy, mostly because of early deaths, were excluded from the Evaluable populations. Two cycles of therapy appear to be the minimum length of treatment for a response. Patients adjudicated to have AML rather than MDS were also excluded from the Evaluable populations, but this exclusion did not influence the response statistics as AML patients responded as well as MDS patients to DAC therapy.

Reviewer's Table. Summary of Overall Response Rates to DAC in MDS (Evaluable Populations)

Response	D-0007 N=56	PHC 97-19 N=62	PHC 95-11 N=48	Total, N=166
Overall (CR + PR)	12 (21%)	23 (40%)	17 (35%)	52 (31%)
CR	6 (11%)	19 (33%)	14 (29%)	39 (23%)
PR	6 (11%)	4 (7%)	3 (6%)	13 (8%)

4. The clinical benefit of DAC-induced responses was normalization of blood counts and bone marrow blast percentages and elimination of the need for transfusions in patients who were transfusion-dependent at baseline. Patients with responses who were pancytopenic but not transfusion-dependent at baseline had normalization of blood counts. Patients with responses who had elevated blast counts in the bone marrow at baseline had normalization of blast percentages.

5. The median time to response to DAC therapy was 89 days in the controlled trial. Responses were long lasting, as shown in Reviewer's table below. Median durations of response were 250 and 266 days in two studies and 146 days in one study, with very wide ranges in all studies.

Reviewer's Table. Duration of Response (ITT Populations)

Duration of Response (days)	D-007	PCH 97-19	PCH 95-11
Median (range)	266 (131-346)	146 (1-545)	250 (78-456)
Mean±SD		148±25	263±21.3

6. Responses occurred in patients with each of the five FAB subtypes of MDS, as shown in the Reviewer's table below. Small numbers of patients in some subtype categories do not permit comparison of response rates between FAB subtypes. Responses occurred at similar frequencies among IPSS Intermediate-1, Intermediate-2 and High Risk patients.

Reviewer's Table. Overall Response Rates (CR + PR) by IPSS and FAB Classifications (ITT Populations)

MDS subtype	D-0007, N=89	PCH 97-19, N=98	PCH 95-11, N=66	Total N=253
FAB Classification				
RA	2/12 (25%)	2/9 (22%)	1/7 (14%)	5/28 (18%)
RARS	0/7 (0%)	1/2 (50%)	-	1/9 (11%)
RAEB	9/47 (20%)	10/34 (29%)	8/26 (31%)	27/107 (25%)
RAEB-t	2/17 (12%)	5/33 (15%)	5/24 (21%)	12/74 (16%)
CMML	1/6 (17%)	4/14 (29%)	2/8 (25%)	7/28 (25%)
IPSS Classif.*				
Low		4/6 (67%)	0/1	4/7 (57%)
INT-1	4/28 (14%)	4/18 (22%)	4/19 (21%)	12/65 (18%)
INT-2	8/38 (21%)	7/14 (50%)	6/25 (24%)	21/77 (27%)
High Risk	3/23 (13%)	9/37 (24%)	7/21 (33%)	19/81 (20%)
Total	89 (100%)	75 (77%)	66 (100%)	

*Not all patients in PCH 97-19 had cytogenetics and IPSS group could not be determined.

7. Responses occurred at about the same rate in all age groups, as shown in Reviewer's table below.

Reviewer's Table. Overall Response Rates (CR + PR) by Age (ITT Populations)

Age group	D-0007, N=89	PCH 97-19, N=98	PCH 95-11, N=66	Total N=253
Age in years, mean (range)	69 (31-85)	70 (51-87)	68 (37-84)	
<65	6/23 (26%)	4/22 (18%)	5/24 (21%)	15/69 (22%)
65-74	7/42 (17%)	11/48 (23%)	5/29 (17%)	23/119 (19%)
≥75	2/24 (8%)	9/28 (31%)	5/13 (38%)	16/65 (25%)

8. Response rates in females were higher in males in two of the studies and equal in one study.

Reviewer's Table. Overall Response Rates (CR + PR) by Gender (ITT Populations)

Gender	D-0007, N=89	PCH 97-19, N=98	PCH 95-11, N=66	Total N=253
Male	7/59 (12%)	18/72 (25%)	7/46 (15%)	32/177 (18%)
Female	8/30 (27%)	6/26 (23%)	8/20 (40%)	22/76 (29%)

9. Analyses of response rates by race by race/ethnicity were not performed because most of the study subjects where White.

10. Response rates were higher in patients with no prior therapy for MDS than in patients with prior therapy, as shown in the Reviewer's table below. *De novo* and secondary MDS patients had the same response rates.

Reviewer's Table. Overall Response Rates - Subgroup Analyses by Prior MDS Therapy and by Type of MDS (ITT Populations)

	D-0007	PCH 97-19	PCH 95-11	Total
Prior MDS Therapy				
Yes	3/27 (11%)	1/11 (9%)	0/1	4/39 (10%)
No	12/62 (19%)	23/87 (27%)	17/65 (26%)	52/214 (24%)
Type of MDS				
De novo	13/77 (17%)			13/77 (17%)
Secondary	2/12 (16%)			2/12 (16%)

11. DAC treatment resulted in a statistically longer median Time to AML or Death than supportive care in IPSS High Risk patients (260 days vs. 79 days, unadjusted p=0.010 by two-sided log-rank test), but not in INT-1 and INT-2 patients.

12. DAC treatment had no effect on overall survival; median survival in the DAC treatment group was 391 days and in the supportive care group, 417 days. In PCH 97-19 study, median survival was 468 days, and in PCH 95-11 study, 401 days.

13. Febrile neutropenia occurred more frequently in DAC-treated patients than in supportive care patients (29% vs. 6%).

14. Rates of Hematological Improvement (CR + PR + HI) were greater and in DAC treatment group (28%) than in supportive care group (6%). This difference was statistically significant ($p < 0.001$). Median duration of improvement was similar in both treatment arms, 253 days in the DAC arm and 212 days in the supportive care arm.

    In PCH 97-19 study, the rate of Hematological Improvement (CR + PR + HI) was 41% (40/98 patients). In PCH 95-11 study, the rate of Hematological Improvement was also 39% (25/66 patients).

15. In Quality of Life analysis, DAC patients had the following statistically superior parameters than supportive care patients: global health status, dyspnea and fatigue. In the supporting studies, performance status did not change during the course of DAC treatment.

16. Cytogenetic evaluation: In the DAC treatment arm, 9/48 (19%) of patients had a major cytogenetic response and 1/48 (2%) had a minor response. Among patients with CR + PR 53% (8/15) had a major cytogenetic response. In the supportive care arm 2 (6%) of patients had a major cytogenetic response. One had HI and one, progressive disease.

There was a lack of correlation between IPSS Cytogenetic Prognostic Group and response to treatment with DAC.

17. The DAC dosage regimen is appropriate for this patient population, since in the controlled study DAC arm patients received 97% of their prescribed doses.

18. Temporary changes in treatment regimen occurred in 35% of patients, either delays of the next cycle (19%), delays of the next cycle and dose reduction (11%) or dose reductions (5%). These changes were due to adverse events.

Limitations of the available data:

1. The statistical plan of two co-primary endpoints (overall response rate and time to AML or death) with statistical significance p values of ≥ 0.024 each was easily met by the ORR endpoint, since spontaneous responses in MDS are rare and did not occur in the supportive care arm of the controlled trial, with resulting p value of < 0.001. However, statistical significance of the treatment results was not met by the increased time to AML or death, a clinical benefit that may be difficult to document in MDS for a number of reasons (e.g. the very wide range of survival, the advanced age of many patients who may die of other illnesses, the heterogeneity of MDS with varied probabilities of transformation to AML and of survival).
2. The criteria for responses in the controlled trial are very similar to the IWG response criteria for MDS, specifying not only the changes in the peripheral blood counts and the bone marrow but the duration of these changes. The earlier response criteria in the Phase II trials differ primarily by the absence of the minimum duration of the hematopoietic changes.
3. The sponsor comments that the rate and durability of response, conversion to a better response, time to AML or death, and survival could have been negatively impacted by the design of the randomized trial. (Patients who achieved a CR, or a PR or an HI by Cycle 4 received only two additional cycles of therapy and then removed from the study.)
4. The above conclusions are based on data as submitted. As described in 4.3 Data Quality and Integrity, some of the data may not be reliable.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

A total of 240 patients with MDS had received DAC in the three primary studies (154 patients in PCH 95-11 and PCH 97-19, and 83 randomized plus 3 crossover patients in the randomized trial D-0007. The dose of DAC was the same in all 3 studies (15 mg/m^2 IV every 8 hours for 3 consecutive days). The 4-hour infusion (in two 2-hour aliquots) in the Phase II studies and the 3-hour infusion in the D-0007 trial did not appear to cause any difference in effectiveness or adverse symptomatology. Data from these studies cannot be fully integrated. The Phase II studies used WHO adverse event grading criteria, the D-0007 trial used NCI CTC. In addition to

these three studies, the sponsor submitted older Phase I/II studies in 129 patients with MDS or AML, in which higher dosing regimens were administered. These studies cannot be pooled because of differences in reporting formats, but the data indicate primary toxicity to be dose-dependent myelosuppression.

7.1.1 Deaths

The number and causes of deaths in study D-0007 are presented in a reviewer's table, which presents the data abbreviated from Sponsor's Table 32.

Reviewer's Table. Causes of Deaths for Patients Receiving Decitabine or Supportive Care

Cause of Death	DAC Observation Period* N=83	Supp. Care Observation Period* N=81	DAC Long-Term FollowUp** N=83	Supp.Care Long-Term FollowUp** N=81	TOTAL DAC N=83	TOTAL Support Care N=81
Total	12 (14%)	18 (22%)	47 (57%)	37 (46%)	59 (71%)	55 (68%)
MDS/AML	2 (2%)	6 (7%)	19 (23%)	17 (21%)	21 (25%)	23 (28%)
DAC Toxicity	0	-	0	-	0	-
Any Infection	5 (6%)	3 (4%)	6 (7%)	4 (5%)	11 (13%)	7 (9%)
Hemorrhage	0	0	2 (2%)	0	2 (2%)	0
Intracranial Hemorrhage	2 (2%)	0	0	1 (1%)	2 (2%)	1 (1%)
Other* **	3 (4%)	7 (9%)	5 (6%)	5 (6%)	8 (10%)	12 (15%)
Not Reported or Unknown	0	2 (2%)	15 (18%)	10 (12%)	15 (18%)	12 (15%)

*Observation period was from the first dose to 56 days after the last study drug dose in the DAC arm, and from one week after randomization to 56 days after study discontinuation in the supportive care arm.
**Long term follow-up was defined as any period following 56-day post-study adverse event observation period.
***Included in the DAC arm: 3 cases of myocardial infarction, two of congestive heart failure, one of renal failure, one of respiratory failure, and one of and complications following surgery. Included in the Supportive Care arm: 3 cases of myocardial infarction, one of congestive heart failure, four of respiratory failure, two of multisystem organ failure, and one of fever.

The overall incidence of death was similar for the two treatment arms. During the study period, there were fewer deaths in the DAC arm than in the supportive Care arm (12 vs. 18), but on long-term follow-up (24 DAC patients and 26 Supportive Care patients) they evened out between the two arms. Of note,

- There were no deaths attributed to DAC toxicity
- There were more deaths during the study in the Supportive Care arm than in the DAC arm
- More patients died of MDS/AML in the Supportive Care arm than in the DAC arm

- Hemorrhagic and cardiovascular events were rare and occurred in both arms with slightly higher frequency in the DAC arm (one case associated with tamoxifen)
- In the long-term follow-up period, disease progression and infection were the most common causes of death in both arms.
- Narratives of deaths and of SAEs were provided in the submission but are not described in the review.

The sponsor presents in Table 33 the relationship between serious adverse events (SAEs) and causes of death.

- Febrile neutropenia is related to MDS/AML (1 case)
- Anemia, neutropenia, febrile neutropenia are related to cardiomyopathy, renal failure, CHF (2 cases)
- Pneumonia is related to infection (1 case)
- MI with CHF are related to MI with CHF (1 case)
- Intracranial hemorrhage is related to intracranial hemorrhage (1 case)
- Febrile neutropenia and myelosuppression are related to infection (1 case)
- Supraventricular tachycardia and subdural hematoma are related to subdural hematoma (1 case)
- Neutropenic fever and dehydration are related to MDS/AML (1 case)
- Pneumonia is related to MDS/AML (1 case)

7.1.2 Other Serious Adverse Events

At least one SAE was reported in 69% of patients in the DAC arm and in 56% of patients in the SC (Supportive Care) arm. The noteworthy differences will be summarized by Sponsor's Table 34.

Table 34 Number of Dacogen Patients with Serious Adverse Events

SOC Serious Adverse Event Preferred Term	Dacogen (N = 83)			Supportive Care (N = 81)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Any Serious Adverse Event	–	–	**57 (69)**	–	–	**45 (56)**
Blood and lymphatic system disorders	–	–	**28 (34)**	–	–	**11 (14)**
Febrile neutropenia	12 (14)	5 (6)	21 (25)	2 (2)	0 (0)	4 (5)
Anaemia NOS	0 (0)	0 (0)	3 (4)	0 (0)	0 (0)	4 (5)
Neutropenia	1 (1)	1 (1)	3 (4)	0 (0)	2 (2)	3 (4)
Thrombocytopenia	0 (0)	1 (1)	2 (2)	0 (0)	1 (1)	2 (2)
Lymphadenopathy	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Leukopenia NOS	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Myelosuppression	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Splenomegaly	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac disorders	–	–	**8 (10)**	–	–	**4 (5)**
Myocardial infarction	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)
Cardiac failure congestive	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
Cardio-respiratory arrest	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	1 (1)
Cardiomyopathy NOS	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	1 (1)
Atrial fibrillation	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac failure NOS	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Supraventricular tachycardia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	–	–	**4 (5)**	–	–	**10 (12)**
Abdominal pain NOS	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)
Gingival bleeding	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gingival pain	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Tongue ulceration	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Upper gastrointestinal haemorrhage	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
General disorders and administrative site conditions	–	–	**18 (22)**	–	–	**8 (10)**

Table 34 Number of Dacogen Patients with Serious Adverse Events (Cont'd)

SOC Serious Adverse Event Preferred Term	Dacogen (N = 83)			Supportive Care (N = 81)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Pyrexia	1 (1)	1 (1)	12 (14)	0 (0)	1 (1)	4 (5)
Chest pain	1 (1)	0 (0)	1 (1)	3 (4)	0 (0)	3 (4)
Intermittent pyrexia	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	2 (2)
Asthenia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Lethargy	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Mucosal inflammation NOS	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Rigors	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Catheter site haemorrhage	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Hepatobiliary disorders	–	–	**1 (1)**	–	–	**0 (0)**
Cholecystitis NOS	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations	–	–	**28 (34)**	–	–	**17 (21)**
Pneumonia NOS	8 (10)	2 (2)	14 (17)	7 (9)	1 (1)	10 (12)
Catheter related infection	2 (2)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)
Cellulitis	2 (2)	0 (0)	2 (2)	2 (2)	0 (0)	4 (5)
Fungal infection NOS	0 (0)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)
Urinary tract infection NOS	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Staphylococcal infection	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Sepsis NOS	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)
Upper respiratory tract infection NOS	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)
Bronchopulmonary aspergillosis	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Peridiverticular abscess	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory tract infection NOS	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Lung infection pseudomonal	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Mycobacterium avian complex infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications	–	–	**1 (1)**	–	–	**1 (1)**
Post procedural pain	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Post procedural haemorrhage	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

Table 34 Number of Dacogen Patients with Serious Adverse Events (Cont'd)

SOC Serious Adverse Event Preferred Term	Dacogen (N = 83)			Supportive Care (N = 81)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Metabolism and nutrition disorders	–	–	**1 (1)**	–	–	**0 (0)**
Dehydration	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	–	–	**1 (1)**	–	–	**0 (0)**
Pain in limb	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Nervous system disorders	–	–	**3 (4)**	–	–	**0 (0)**
Intracranial haemorrhage NOS	1 (1)	1 (1)	3 (4)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	–	–	**2 (2)**	–	–	**0 (0)**
Confusional state	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Mental status changes	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Renal and urinary disorders	–	–	**2 (2)**	–	–	**3 (4)**
Renal failure	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Urethral haemorrhage	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	–	–	**10 (12)**	–	–	**9 (11)**
Dyspnoea	2 (2)	2 (2)	5 (6)	1 (1)	3 (3)	4 (5)
Hypoxia	3 (4)	0 (0)	3 (4)	1 (1)	0 (0)	2 (2)
Hemoptysis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Lung infiltration NOS	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Pulmonary embolism	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory arrest	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Pulmonary mass	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	–	–	**1 (1)**	–	–	**1 (1)**
Swelling face	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Vascular disorders	–	–	**1 (1)**	–	–	**2 (2)**
Hypotension NOS	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

Source: Table 14.3.2.4 Listing of Serious Adverse Events – All Patients; Table 14.3.2.5 Summary of Serious Adverse Events – All Patients; Table 14.3.2.6 Numbers of Patients with Any On-Study Serious Adverse Event

Reviewer's Comments on Table 34:

- Under Blood and lymphatic system disorders, more patients in the DAC arm had SAEs than in the Supportive Care (SC) arm (34% vs. 14%). Twenty-one (25%) of DAC arm patients had febrile neutropenia, of whom 12 had grade 3 and 5 had grade 4, vs. 4 SC patients (5%), of whom 2 had grade 3 and none had grade 4. The differences between other SAEs (anemia, neutropenia, thrombocytopenia, lymphadenopathy, etc.) were small.

- Under Cardiac disorders, more patients in the DAC arm had SAEs than in the SC arm (10% vs. 5%). The main differences were 2 patients with MI's in the DAC arm, one with atrial fibrillation, one with cardiac failure and one with SVT in the DAC arm vs. none in the SC arm.

- Under Gastrointestinal disorders, more patients in the SC arm had SAEs than in the DAC arm (12% vs. 5%). Most SAEs were < grade 3 in both arms.

- Under General disorders, more patients had fever 12 (14%) in the DAC arm vs. 4 (5%) in the SC arm. Other disorders were reported by single patients.

- Under Hepatobiliary disorders, one patient in the DAC arm had cholecystitis vs. none in the SC arm.

- Under Infections and infestations, more patients in the DAC arm reported SAEs than in the SC arm (34% vs. 21%). These ranged from pneumonia, 14 (17%) in the DAC arm vs. 10 (12%) in the SC arm, and catheter related infections, 4 (5%) in the DAC arm vs. none in the SC arm, to two or one patients with a wide variety of bacterial and fungal infections (Mycobacterium avium, pseudomonas lung infection, aspergillosis, etc).

- Under Nervous System disorders, there were 3 patients (4%) in the DAC arm with intracranial hemorrhage vs. none in the SC arm.

- Metabolism, renal and urinary disorders, respiratory, skin, vascular SAEs were balanced between the two arms.

- There were two patients in the DAC arm who had mental status changes vs. none in the SC arm.

DAC was temporarily suspended because of neutropenia, pulmonary congestion, atrial fibrillation, central line infection and febrile neutropenia (Sponsor's Table 36).

DAC dose was reduced because of thrombocytopenia (4%), neutropenia (2%), tachycardia (1%), pharyngitis (1%), anemia (1%), lethargy (1%), edema (1%), and depression (1%).

Numerically the above data are shown in sponsor's Table 26, slightly modified by the reviewer for clarity.

Reviewer's Table. Patients Experiencing Dose Reductions and Dosing Delays

Decitabine Dose Reduction and/or Delay	Number of Patients (%)
No Dose Reduction & No Dose Delay	54 (65%)
No Dose Reduction. Delay of Dose	16 (19%)
Dose Reduction. No Dose Delay	4 (5%)
Dose Reduction & Dose Delay	9 (11%)

7.1.3 Dropouts and Other Significant Adverse Events

Permanent discontinuation of DAC occurred in 8 patients because of

- thrombocytopenia (2 patients),
- lymphadenopathy,
- neutropenia,
- pneumonia,
- *M. avium* infection,
- cardiac arrest,
- elevated bilirubin and elevated SGPT (2 patients).

Permanent discontinuation in SC arm occurred in 2 patients because of

- COPD and
- dyspnea (source: Sponsor's Table 36).

Overlaps. Three patients who had permanent discontinuation (because of thrombocytopenia in two patients and pneumonia in one) also had dose reductions and temporary suspensions because of other adverse events (anemia, pulmonary congestion, neutropenia) listed above.

Overall profile of dropouts. There is no particular profile of patients who dropped out of the study.

Adverse events associated with dropouts. Described above.

Other significant adverse events. Described below under composite table of adverse events.

7.1.4 *Other Search Strategies.* Literature searches in PubMed.

7.1.5 *Common Adverse Events.* As stated above myelosuppression and gastrointestinal events were the most common adverse events in all studies with DAC.

Eliciting adverse events data in the development program.

D-0007 trial used NCI CTC. While Phase II PCH 95-11 and PCH 97-19 used WHO grading criteria. Older Phase I/II studies' data cannot be combined with the NCI CTC and WHO because of differences in reporting formats. However, the safety profile that emerges from these studies is the same as in the later studies. Pediatric studies in leukemia used cytotoxic doses four- to ten-times the doses used in MDS; the major toxicity in these studies was dose-dependent myelosuppression. Similar conclusions were reached in studies with solid tumors, in which high doses were used as well.

Appropriateness of adverse event categorization and preferred terms. Adverse events shown in the table below use MedDRA terminology.

Incidence of common adverse events

The randomized controlled study D-0007 provides the best comparative data on DAC. It should be emphasized that patients were taken off DAC treatment if hematological recovery exceeded 10 weeks. The decreasing numbers of patients with successive cycles reflects the study design whereby patients who had CR, stable disease or progressive disease were taken off study at designated time points. The decreasing numbers of patients exposed to successive cycles of DAC therapy is not evidence of cumulative toxicity or of decreasing tolerability.

Common adverse event tables

Adverse events that occurred in 5% or more patients in the DAC arm in Study D-0007 are shown in Sponsor's table 28 below. Adverse events are classified by System, Organ, Class (SOC) MedDRA classification and also by grades 3 ("severe") or 4 ("life-threatening") in severity. A 5% point difference was used to differentiate adverse events that may be related to MDS or to DAC. Study D-0007 permits a comparison between DAC and Supportive Care.

Reviewer's Comments:

1. *Neutropenia, thrombocytopenia, febrile neutropenia, leukopenia were prominently more common in the DAC arm than in the SC arm.*
2. *Gastrointestinal disorders (generally of less than grade 3), including nausea, constipation, diarrhea, vomiting, abdominal pain, stomatitis, oral patechiae, dyspepsia, ascites were also much more common in the DAC arm than in the SC arm.*
3. *Among general disorders, fever, peripheral edema, lethargy, pain were more common in the DAC arm than in the SC arm, but the rest of the symptoms are fairly evenly distributed.*
4. *Pneumonia, cellulites, candidal infections, catheter related infections, staph infections were more common in the DAC group than in the SC group.*
5. *A variety of pains (arthralgia, pain in limb, back pain, chest wall pain, muscular discomfort, myalgias) were more common on the DAC group than in the SC group.*
6. *Headaches, dizziness, hypoesthesia were more common on the DAC group than in the SC group.*
7. *Insomnia, confusional state, but not depression or anxiety, were more common in the DAC group than in the SC group.*
8. *Cough, crackles in the lungs, and pharyngitis were more common in the DAC arm than in the SC arm, but a variety of respiratory symptoms occurred at the same frequency.*
9. *There were more ecchymoses and patechiae, pallor, rashes, erythemas, alopecias among skin disorders in the DAC group than in the SC group.*
10. *Cardiac murmurs were about evenly distributed between arms.*
11. *There were differences between groups in the following laboratory values: increased BUN, decreased albumin, decreased total protein, increased electrolytes, LDH, and decreased bilirubin.*
12. *Most laboratory values were not much different between the two arms.*

The sponsor presented changes in adverse events during the ensuing cycles.

1. Neutropenia, thrombocytopenia, anemia continued to be common during the first 6 cycles.
2. Gastrointestinal disorders decreased after the first 2 cycles.
3. Fever decreased after the first 3 cycles.
4. Electrolyte disorders decreased after the first cycle.
5. In general, most of the adverse events decreased after the first 3 cycles.

Table 28 Adverse Events ≥ 5% Incidence by System Organ Classification and Grade

SOC Heading Preferred MedDRA Term	All Adverse Events						Treatment-Related Adverse Events
	Dacogen N = 83 (%)			Supportive Care N = 81 (%)			Dacogen N = 83 (%)
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	All Grades N (%)
Any Adverse Event			**83 (100)**			**79 (98)**	**82 (98)**
Blood and lymphatic system disorders	–	–	**80 (96)**	–	–	**69 (85)**	**76 (92)**
Neutropenia	8 (10)	64 (77)	75 (90)	20 (25)	20 (25)	58 (72)	69 (83)
Thrombocytopenia	18 (22)	52 (63)	74 (89)	22 (27)	13 (16)	64 (79)	67 (81)
Anaemia NOS	9 (11)	1 (1)	68 (82)	11 (14)	1 (1)	60 (74)	45 (54)
Febrile neutropenia	14 (17)	5 (6)	24 (29)	3 (4)	0 (0)	5 (6)	18 (22)
Leukopenia NOS	7 (8)	12 (14)	23 (28)	4 (5)	2 (2)	11 (14)	19 (23)
Lymphadenopathy	0 (0)	0 (0)	10 (12)	1 (1)	0 (0)	6 (7)	0 (0)
Leukocytosis	0 (0)	1 (1)	9 (11)	0 (0)	0 (0)	11 (14)	0 (0)
Splenomegaly	0 (0)	0 (0)	6 (7)	2 (2)	0 (0)	7 (9)	2 (2)
Thrombocythaemia	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)	3 (4)
Cardiac disorders	–	–	**27 (33)**	–	–	**17 (21)**	**6 (7)**
Tachycardia NOS	1 (1)	0 (0)	7 (8)	1 (1)	0 (0)	8 (10)	1 (1)
Pulmonary oedema NOS	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)	1 (1)

SOC Heading Preferred MedDRA Term	All Adverse Events						Treatment-Related Adverse Events
	Dacogen N = 83 (%)			Supportive Care N = 81 (%)			Dacogen N = 83 (%)
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	All Grades N (%)
Congenital, familial and genetic disorders	–	–	**2 (2)**	–	–	**0 (0)**	0 (0)
Ear and labyrinth disorders	–	–	**12 (14)**	–	–	**7 (9)**	**1 (1)**
Endocrine disorders	–	–	**3 (4)**	–	–	**1 (1)**	**0 (0)**
Eye disorders	–	–	**20 (24)**	–	–	**11 (14)**	**5 (6)**
Vision blurred	1 (1)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)	2 (2)
Gastrointestinal disorders	–	–	**71 (86)**	–	–	**45 (56)**	**44 (53)**
Nausea	1 (1)	0 (0)	35 (42)	3 (4)	0 (0)	13 (16)	18 (22)
Constipation	2 (2)	0 (0)	29 (35)	1 (1)	0 (0)	11 (14)	7 (8)
Diarrhoea NOS	0 (0)	0 (0)	28 (34)	1 (1)	1 (1)	13 (16)	13 (16)
Vomiting NOS	0 (0)	0 (0)	21 (25)	0 (0)	0 (0)	7 (9)	7 (8)
Abdominal pain NOS	2 (2)	0 (0)	12 (14)	3 (4)	0 (0)	5 (6)	3 (4)
Oral mucosal Petechiae	2 (2)	0 (0)	11 (13)	1 (1)	0 (0)	4 (5)	4 (5)
Stomatitis	0 (0)	0 (0)	10 (12)	0 (0)	0 (0)	5 (6)	6 (7)
Dyspepsia	1 (1)	0 (0)	10 (12)	0 (0)	0 (0)	1 (1)	0 (0)
Ascites	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)	2 (2)	2 (2)
Gingival bleeding	1 (1)	0 (0)	7 (8)	0 (0)	0 (0)	5 (6)	1 (1)
Haemorrhoids	0 (0)	0 (0)	7 (8)	0 (0)	0 (0)	3 (4)	0 (0)
Loose stools	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	3 (4)	2 (2)
Tongue ulceration	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	2 (2)	4 (5)
Dysphagia	2 (2)	0 (0)	5 (6)	0 (0)	1 (1)	2 (2)	2 (2)
Oral soft tissue disorder NOS	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	1 (1)	4 (5)
Abdominal pain lower	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	4 (5)	0 (0)
Lip ulceration	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	3 (4)	3 (4)
Abdominal distension	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)	0 (0)

SOC Heading Preferred MedDRA Term	All Adverse Events						Treatment-Related Adverse Events
	Dacogen N = 83 (%)			Supportive Care N = 81 (%)			Dacogen N = 83 (%)
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	All Grades N (%)
Abdominal pain upper	0 (0)	0 (0)	4 (5)	0 (0)	0 (C)	1 (1)	1 (1)
Gastrooesophageal reflux disease	0 (0)	0 (0)	4 (5)	0 (0)	0 (C)	0 (0)	0 (0)
Glossodynia	0 (0)	0 (0)	4 (5)	0 (0)	0 (C)	0 (0)	1 (1)
General disorders and administrative site disorders	–	–	**72 (87)**	–	–	**65 (80)**	**31 (37)**
Pyrexia	4 (5)	1 (1)	44 (53)	0 (0)	1 (1)	23 (28)	13 (16)
Fatigue	5 (6)	2 (2)	40 (48)	9 (11)	1 (1)	39 (48)	15 (18)
Oedema peripheral	3 (4)	0 (0)	21 (25)	0 (0)	0 (C)	13 (16)	3 (4)
Asthenia	7 (8)	1 (1)	19 (23)	4 (5)	1 (1)	21 (26)	3 (4)
Rigors	1 (1)	0 (0)	18 (22)	0 (0)	0 (C)	14 (17)	1 (1)
Oedema NOS	0 (0)	0 (0)	15 (18)	0 (0)	0 (C)	5 (6)	1 (1)
Pain NOS	3 (4)	0 (0)	11 (13)	0 (0)	0 (C)	5 (6)	0 (0)
Lethargy	2 (2)	1 (1)	10 (12)	0 (0)	0 (C)	3 (4)	3 (4)
Chest pain	3 (4)	0 (0)	9 (11)	4 (5)	0 (C)	9 (11)	1 (1)
Tenderness NOS	0 (0)	0 (0)	9 (11)	0 (0)	0 (C)	0 (0)	0 (0)
Fall	1 (1)	0 (0)	7 (8)	1 (1)	0 (C)	3 (4)	1 (1)
Chest discomfort	1 (1)	0 (0)	6 (7)	0 (0)	0 (C)	3 (4)	0 (0)
Intermittent pyrexia	0 (0)	0 (0)	5 (6)	1 (1)	0 (C)	3 (4)	2 (2)
Malaise	0 (0)	0 (0)	4 (5)	0 (0)	0 (C)	1 (1)	0 (0)
Crepitations NOS	0 (0)	0 (0)	4 (5)	0 (0)	0 (C)	1 (1)	1 (1)
Catheter site erythema	0 (0)	0 (0)	4 (5)	0 (0)	0 (C)	1 (1)	0 (0)
Catheter site pain	0 (0)	0 (0)	4 (5)	0 (0)	0 (C)	0 (0)	0 (0)
Injection site swelling	0 (0)	0 (0)	4 (5)	0 (0)	0 (C)	0 (0)	0 (0)
Hepatobiliary Disorders	–	–	**22 (27)**	–	–	**17 (21)**	**4 (5)**
Hyperbilirubinaemia	4 (5)	1 (1)	12 (14)	0 (0)	0 (C)	4 (5)	3 (4)
Hepatomegaly	1 (1)	0 (0)	8 (10)	1 (1)	0 (C)	10 (12)	1 (1)

SOC Heading Preferred MedDRA Term	All Adverse Events						Treatment-Related Adverse Events
	Dacogen N = 83 (%)			Supportive Care N = 81 (%)			Dacogen N = 83 (%)
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	All Grades N (%)
Immune system disorders	–	–	**2 (2)**	–	–	**2 (2)**	**0 (0)**
Infections and Infestations	–	–	**60 (72)**	–	–	**43 (53)**	**19 (23)**
Pneumonia NOS	11 (13)	2 (2)	18 (22)	6 (7)	2 (2)	11 (14)	8 (10)
Cellulitis	2 (2)	1 (1)	10 (12)	2 (2)	0 (0)	6 (7)	2 (2)
Candidal infection NOS	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)	1 (1)	2 (2)
Catheter related infection	2 (2)	0 (0)	7 (8)	0 (0)	0 (0)	0 (0)	1 (1)
Urinary tract infection NOS	1 (1)	0 (0)	6 (7)	1 (1)	0 (0)	1 (1)	2 (2)
Staphylococcal infection	2 (2)	1 (1)	6 (7)	0 (0)	0 (0)	0 (0)	1 (1)
Upper respiratory tract infection NOS	0 (0)	0 (0)	5 (6)	3 (4)	0 (0)	7 (9)	0 (0)
Oral candidiasis	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	2 (2)	3 (4)
Herpes simplex	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	4 (5)	2 (2)
Sinusitis NOS	0 (0)	0 (0)	4 (5)	1 (1)	0 (0)	2 (2)	1 (1)
Bacteraemia	2 (2)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)	1 (1)
Injury, poisoning and procedural complications	–	–	**20 (24)**	–	–	**12 (15)**	**2 (2)**
Transfusion reaction	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	3 (4)	0 (0)
Abrasion NOS	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)	0 (0)
Investigations	–	–	**59 (71)**	–	–	**38 (47)**	**13 (16)**
Cardiac murmur NOS	0 (0)	0 (0)	13 (16)	0 (0)	0 (0)	9 (11)	2 (2)
Alanine aminotransferase increased	1 (1)	0 (0)	10 (12)	0 (0)	0 (0)	10 (12)	1 (1)
Blood alkaline phosphatase NOS increased	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	7 (9)	3 (4)
Aspartate aminotransferase increased	1 (1)	0 (0)	8 (10)	0 (0)	0 (0)	7 (9)	1 (1)
Blood urea increased	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)	1 (1)	0 (0)

SOC Heading Preferred MedDRA Term	All Adverse Events						Treatment-Related Adverse Events
	Dacogen N = 83 (%)			Supportive Care N = 81 (%)			Dacogen N = 83 (%)
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	All Grades N (%)
Blood lactate dehydrogenase increased	0 (0)	0 (0)	7 (8)	0 (0)	0 (0)	5 (6)	2 (2)
Blood albumin decreased	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	0 (0)	2 (2)
Blood bicarbonate increased	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	1 (1)	2 (2)
Blood chloride decreased	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	1 (1)	2 (2)
Blood bilirubin increased	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	4 (5)	2 (2)
Blood chloride increased	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	4 (5)	1 (1)
Protein total decreased	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	3 (4)	1 (1)
Blood bicarbonate decreased	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)	1 (1)
Blood bilirubin decreased	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)	0 (0)
Metabolism and nutrition disorders	–	–	**65 (78)**	–	–	**49 (60)**	**21 (25)**
Hyperglycaemia NOS	7 (8)	0 (0)	27 (33)	1 (1)	0 (0)	16 (20)	2 (2)
Hypocalcaemia	0 (0)	1 (1)	21 (25)	1 (1)	1 (1)	20 (25)	6 (7)
Hypoalbuminaemia	2 (2)	0 (0)	20 (24)	1 (1)	0 (0)	14 (17)	6 (7)
Hypomagnesaemia	0 (0)	0 (0)	20 (24)	1 (1)	0 (0)	6 (7)	2 (2)
Hypokalaemia	2 (2)	0 (0)	18 (22)	4 (5)	0 (0)	10 (12)	3 (4)
Hyponatraemia	1 (1)	0 (0)	16 (19)	1 (1)	0 (0)	13 (16)	4 (5)
Appetite decreased NOS	0 (0)	0 (0)	13 (16)	1 (1)	1 (1)	12 (15)	3 (4)
Anorexia	0 (0)	0 (0)	13 (16)	1 (1)	0 (0)	8 (10)	5 (6)
Hyperkalaemia	0 (0)	0 (0)	11 (13)	1 (1)	0 (0)	3 (4)	4 (5)
Dehydration	1 (1)	0 (0)	5 (6)	1 (1)	0 (0)	4 (5)	1 (1)
Musculoskeletal and connective tissue disorders	–	–	**51 (61)**	–	–	**33 (41)**	**3 (4)**
Arthralgia	3 (4)	0 (0)	17 (20)	0 (0)	0 (0)	8 (10)	1 (1)
Pain in limb	1 (1)	0 (0)	16 (19)	1 (1)	0 (0)	8 (10)	0 (0)
Back pain	2 (2)	0 (0)	14 (17)	0 (0)	0 (0)	5 (6)	1 (1)

SOC Heading Preferred MedDRA Term	All Adverse Events						Treatment-Related Adverse Events
	Dacogen N = 83 (%)			Supportive Care N = 81 (%)			Dacogen N = 83 (%)
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	All Grades N (%)
Chest wall pain	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	1 (1)	0 (0)
Musculoskeletal discomfort	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Muscle cramp	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	4 (5)	0 (0)
Myalgia	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)	1 (1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	–	–	**5 (6)**	–	–	**4 (5)**	**1 (1)**
Nervous system disorders	–	–	**46 (55)**	–	–	**26 (32)**	**13 (16)**
Headache	2 (2)	0 (0)	23 (28)	0 (0)	0 (0)	11 (14)	8 (10)
Dizziness	0 (0)	0 (0)	15 (18)	2 (2)	0 (0)	10 (12)	2 (2)
Hypoaesthesia	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	1 (1)	1 (1)
Psychiatric disorders	–	–	**36 (43)**	–	–	**26 (32)**	**6 (7)**
Insomnia	0 (0)	0 (0)	23 (28)	0 (0)	0 (0)	11 (14)	4 (5)
Confusional state	1 (1)	0 (0)	10 (12)	0 (0)	0 (0)	3 (4)	2 (2)
Depression	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	11 (14)	2 (2)
Anxiety	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	8 (10)	0 (0)
Renal and urinary disorders	–	–	**21 (25)**	–	–	**14 (17)**	**6 (7)**
Dysuria	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	3 (4)	2 (2)
Urinary frequency	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)	1 (1)
Reproductive system and breast disorders	–	–	**5 (6)**	–	–	**4 (5)**	**2 (2)**
Respiratory, thoracic and mediastinal disorders	–	–	**65 (78)**	–	–	**52 (64)**	**17 (20)**
Cough	0 (0)	0 (0)	33 (40)	0 (0)	0 (0)	25 (31)	5 (6)
Dyspnoea NOS	3 (4)	3 (4)	23 (28)	5 (6)	5 (6)	25 (31)	2 (2)
Pharyngitis	2 (2)	0 (0)	13 (16)	0 (0)	0 (0)	6 (7)	3 (4)
Epistaxis	0 (0)	0 (0)	12 (14)	1 (1)	0 (0)	15 (19)	3 (4)
Crackles lung	0 (0)	0 (0)	12 (14)	0 (0)	0 (0)	1 (1)	1 (1)

SOC Heading Preferred MedDRA Term	All Adverse Events						Treatment-Related Adverse Events
	Dacogen N = 83 (%)			Supportive Care N = 81 (%)			Dacogen N = 83 (%)
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	All Grades N (%)
Pleural effusion	1 (1)	0 (0)	8 (10)	2 (2)	0 (0)	9 (11)	2 (2)
Breath sounds decreased	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)	7 (9)	0 (0)
Hypoxia	5 (6)	0 (0)	8 (10)	1 (1)	1 (1)	4 (5)	1 (1)
Rales	0 (0)	0 (0)	7 (8)	0 (0)	0 (0)	2 (2)	0 (0)
Nasal congestion	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	7 (9)	0 (0)
Wheezing	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	7 (9)	0 (0)
Haemoptysis	1 (1)	0 (0)	5 (6)	0 (0)	0 (0)	6 (7)	2 (2)
Nasopharyngitis	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	6 (7)	2 (2)
Lung infiltration NOS	1 (1)	0 (0)	4 (5)	2 (2)	1 (1)	5 (6)	1 (1)
Dyspnea exertional	0 (0)	0 (0)	4 (5)	1 (1)	0 (0)	4 (5)	1 (1)
Postnasal drip	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	2 (2)	1 (1)
Skin and subcutaneous tissue disorders	–	–	**68 (82)**	–	–	**47 (58)**	**23 (28)**
Contusion	0 (0)	0 (0)	20 (24)	0 (0)	0 (0)	20 (25)	5 (6)
Ecchymosis	1 (1)	0 (0)	18 (22)	0 (0)	0 (0)	12 (15)	3 (4)
Rash NOS	0 (0)	0 (0)	16 (19)	0 (0)	0 (0)	7 (9)	6 (7)
Erythema	0 (0)	0 (0)	12 (14)	0 (0)	0 (0)	5 (6)	1 (1)
Skin lesion NOS	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	3 (4)	2 (2)
Pruritis	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	2 (2)	2 (2)
Alopecia	0 (0)	0 (0)	7 (8)	0 (0)	0 (0)	1 (1)	5 (6)
Night sweats	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	7 (9)	1 (1)
Sweating increased	1 (1)	0 (0)	6 (7)	0 (0)	0 (0)	7 (9)	0 (0)
Urticaria NOS	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	1 (1)	2 (2)
Swelling face	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Social circumstances	–	–	**0 (0)**	–	–	**1 (1)**	**0 (0)**
Surgical and medical procedures	–	–	**4 (5)**	–	–	**6 (7)**	**0 (0)**
Vascular disorders	–	–	**51 (61)**	–	–	**30 (37)**	**14 (17)**
Petechiae	2 (2)	0 (0)	32 (39)	1 (1)	0 (0)	13 (16)	10 (12)

SOC Heading Preferred MedDRA Term	All Adverse Events						Treatment-Related Adverse Events
	Dacogen N = 83 (%)			Supportive Care N = 81 (%)			Dacogen N = 83 (%)
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	All Grades N (%)
Pallor	0 (0)	0 (0)	19 (23)	0 (0)	0 (0)	10 (12)	2 (2)
Hypotension NOS	1 (1)	0 (0)	5 (6)	0 (0)	1 (1)	4 (5)	1 (1)
Hypertension NOS	0 (0)	0 (0)	4 (5)	1 (1)	0 (0)	8 (10)	0 (0)
Haematoma NOS	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	3 (4)	0 (0)

Source: Table 14.3.1.3 Summary of Adverse Events – All Patients ; Table 14.3.1.4 Numbers of Patients with Any On-Study Adverse Event; Table 14.3.1.5 Numbers of Patients with Any On-Study Adverse Events Related to Treatment; Table 14.3.1.6 Summary of Adverse Events – Events Judged Related to Study Drug; Appendix 16.2.7.1 Listing of Adverse Events–All Patients; Appendix 16.2.7.3 Listing of Adverse Events – Events Judged Related to Study Drug

Sponsor's Table 12 compares adverse events in the DAC arm to the DAC treatment in Studies PCH 95-11 and PCH 97-19. There are similarities and differences between the D-0007 trial and the Phase II studies. The sponsor is at a loss to explain the differences, especially as the same DAC regimen was used the same patient population.

Differences:

- Blood and Lymphatic System. Much higher incidence of neutropenia (83% vs. 9%), thrombocytopenia (81% vs. 6%), anemia (54% vs. vs. 4%), febrile neutropenia (22% vs. 14%), and leukopenia (23% vs. 2%) in the controlled study than in the Phase II studies.
- Infections/Infestations/Pyrexia. Lower incidence pyrexia (16% vs. 36%), herpetic infections (11% vs. 2%) in the controlled study than in the Phase II studies.
- Vascular disorders (phlebitis), hemorrhage, epistaxis. Much lower incidence of vascular disorders (17% vs. 32%), epistaxis (4% vs. 12%), hemorrhage (0% vs. 16%) in the controlled study than in the Phase II studies.
- Metabolism and nutrition. Disorders are higher in the controlled study (25% vs. 14%).

Similarities:

- Gastrointestinal disorders, fatigue, nervous system disorders, laboratory studies, skin and subcutaneous tissues have about the same incidence in all studies.

Table 12 Adverse Events (≥10%) Related to Treatment

MedDRA SOC Adverse Event	D0007 N=83 (%)	PCH 95-11 & PCH 97-19 Combined N=155 (%)
Blood and Lymphatic System	76 (92)	44 (28)
Neutropenia	69 (83)	14 (9)
Thrombocytopenia	67 (81)	10 (6)
Anemia	45 (54)	6 (-)
Febrile Neutropenia	18 (22)	21 (14)
Leukopenia	19 (23)	3 (2)
Gastrointestinal Disorders	44 (53)	83 (54)
Nausea	18 (22)	46 (30)
Diarrhea	13 (16)	17 (11)
Vomiting	7 (8)	15 (10)
Abdominal pain	3 (4)	12 (8)
General Disorders	31 (37)	88 (57)
Pyrexia	13 (16)	56 (36)
Fatigue	15 (18)	24 (15)
Infections/Infestations	19 (23)	60 (39)
Pneumonia	8 (10)	20 (13)
Herpes simplex	2 (2)	17 (11)
Investigations	13 (16)	16 (10)
Metabolism and Nutrition	21 (25)	21 (14)
Nervous System	13 (16)	28 (18)
Headache	8 (10)	15 (10)
Respiratory Disorders	17 (20)	56 (36)
Epistaxis	3(4)	18 (12)
Cough	5 (6)	14 (9)
Skin and Subcutaneous Tissue	23 (28)	37(24)
Vascular Disorders	14 (17)	50 (32)
Petechiae	10 (12)	13 (8)
Hemorrhage	0	25 (16)

Identifying common and drug-related adverse events

The above analysis described differences in incidence between the DAC arm and the SC arm. Higher prevalence of adverse events, when present, in the DAC arm is presumed to be drug-related. The sponsor used 5% difference to differentiate between drug-related and non-drug-related events.

7.1.6 Less Common Adverse Events

Adverse events in MDS and DAC therapy are encountered by virtually 100% of patients. The cut-off for the above tables (5%) appears to be reasonable.

Laboratory Findings. Described above under adverse events.

Overview of laboratory testing in the development program. Laboratory testing is described in the description of the study protocol above.

Selection of studies and analyses for drug-control comparisons of laboratory values. D-0007 Trial is the only controlled trial and lasted sufficiently long for drug-control comparisons.

Standard analyses and explorations of laboratory data. The drug-control analysis is presented above. A comparison of the DAC arm in the D-0007 trial is contrasted to the combined data from PCH 95-11 and PCH 97-19 (Sponsor's Table 12 from Module 2). Analyses focused on measures of central tendency. The key laboratory parameters were hematologic (both bone marrow and peripheral blood data). Since the response rates to DAC were low (15%-20%) and 80%-85% of patients in the decitabine treatment group continued to decline, a central tendency analysis would not lead to clarification of drug action.

Analyses focused on outliers or shifts from normal to abnormal. In MDS, by definition, hematologic values are abnormal at baseline. Hematological values decline further with DAC treatment until there is a response. Other laboratory values become abnormal as a result of adverse events and pre-morbid state. They do not reflect drug effects.

Marked outliers and dropouts for laboratory abnormalities. The following laboratory abnormalities led to permanent discontinuation of DAC: thrombocytopenia (2 patients), neutropenia (1 patient), and elevated bilirubin and SGPT (2 patients).

Additional analyses and explorations. Dose reductions and dose delays are described above.

Special assessments. No special assessments were carried out. Hepatic abnormalities were minor and transitory with continued treatment, except in the two patients noted above, who had DAC discontinued.

7.1.7 Vital Signs. Analysis of vital signs was not carried out, as they changed only as a result of intercurrent illness, such as dehydration with gastrointestinal adverse events.

Overview of vital signs testing in the development program. Vital signs were measured at each visit, but were not key indicators in the development program.

Selection of studies and analyses for overall drug-control comparisons. The only controlled study was D-0007.

Standard analyses and explorations of vital signs data. No such analysis was carried out, as it is not germane to a drug of this class.

Analyses focused on measures of central tendencies. No analyses were carried out for reasons stated above.

Analyses focused on outliers or shifts from normal to abnormal. No analyses were carried out for reasons stated above.

Marked outliers and dropouts for vital sign abnormalities. Stated above.

Additional analyses and explorations. No analyses were carried out for reasons stated above.

7.1.8 Electrocardiograms (ECGs)

Overview of ECG testing in the development program, including brief review of preclinical results. ECGs were obtained at baseline, but no special testing was carried out during the development program. QTc testing was neither performed nor requested to be performed. There were no signals suggesting that DAC is arrythmogenic. In the D-0007 study, there were three myocardial infarctions in the decitabine arm and three, in the supportive care arm. One patient who had atrial fibrillation at study entry that was controlled with a calcium channel blocker and digoxin. The AF was present throughout the study but was under control. One patient had AF at baseline and was treated with diltiazem, a beta-blocker and amiodarone. A third patient had tachycardia and syncope. AF was not reported during the study, which lasted only one cycle. The patient had onset of AF 6 weeks after the last dose of DAC. There were no sudden deaths in either arm during the study period. DAC has been in development for > 30 years without evidence of arrhythmogenic effect.

7.1.9 Immunogenicity

Decitabine is a deoxyribonucleotide analog that has not been described as immunogenic since its synthesis over 40 years ago.

7.1.10 Human Carcinogenicity

Decitabine is not listed as a known or reasonably anticipated to human carcinogen in the 11th Report on Carcinogens by the National Toxicology Program (2004) (http://ntp.niehs.nih.gov). However, azacitidine is listed as a reasonably anticipated human carcinogen. Thus, it is possible that decitabine may fall into the same category. National Toxicology Program has been contacted for response.

7.1.11 Special Safety Studies

Only mild and transient elevations of liver function tests were noted. There were no deaths due to hepatic or renal failure.

7.1.12 *Withdrawal Phenomena and/or Abuse Potential.* Not applicable.

7.1.13 *Human Reproduction and Pregnancy Data.* Exposure in pregnant patients has not been reported. All studies exclude pregnant women or me and women not practicing contraception.

7.1.14 *Assessment of Effect on Growth.* Early studies with DAC involved pediatric patients with acute leukemia. Effects on growth have not been reported in humans.

7.1.15 *Overdose Experience.* Early studies with DAC used much higher (5- to 10-fold) doses in patients with solid tumors than doses used in treatment of MDS. There were no overdoses in the three trials in this NDA.

7.1.16 *Postmarketing Experience.* Decitabine has not been marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

Treatment emergent adverse events, defined in this NDA as all adverse events, were reported by 100% of patients in the DAC arm (83/83 patients) and by 98% of patients in the supportive care arm (79/81 patients).

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 240 patients with MDS have received DAC in the three primary studies (83 patients who received DAC as a result of being randomized to the DAC treatment arm in the Phase III D-0007 trial, 3 patients who crossed over from the supportive care arm to DAC in D-0007, and 154 patients treated one or more times in the Phase II studies PCH 95-11 and PCH 97-19 [11 patients re-entered PCH 97-19 study after relapse following DAC treatment, one patient re-entered the study without a relapse]). All three studies used 15 mg/m^2 every 8 hours for three consecutive days for a total of nine doses per course. This dose was infused over 4 hours (in two-hourly aliquots) in the Phase II studies. Since these infusions were well tolerated, a single 3-hour infusion was used in the Phase III trial.

The number of courses administered in the controlled trial is shown below in Sponsor's Table 9. About 70% of patients received 2 cycles of DAC (the minimum for a response to occur) and only 30% received 5 cycles.

Table 9 Exposure to Dacogen or Supportive Care by Cycle

Cycle	Dacogen (N = 89)		Supportive Care (N = 81)	
	No. of Patients Completed	Percent of Patients Completed	No. of Patients Completed	Percent of Patients Completed
Cycle 1	83	93%	75	93%
Cycle 2	64	72%	61	75%
Cycle 3	47	53%	41	51%
Cycle 4	38	43%	30	37%
Cycle 5	27	30%	25	31%
Cycle 6*	23	26%	20	25%
Cycle 7	9	10%	6	7%
Cycle 8	7	8%	4	5%
Cycle 9	1	1%	1	1%
Cycle 10	0	0%	0	0%

*Two (2) patients randomized to Dacogen were still participating in the study following six cycles at database lock.

Number of cycles as reflected by investigator at End of Study. Six Dacogen patients were not treated and six Supportive Care patients withdrew before completion of the first 6-week cycle.

Patient exposure was similar in the Phase II studies PCH 95-11 and PCH 97-19. However, the sponsor notes that data from the three studies cannot be fully integrated because of the differences in data collection procedures and in grading systems. The Phase II studies used WHO grading criteria, while the Phase III D-0007 trial used NCI CTC.

Still older Phase I/II studies in 129 patients with MDS or AML had higher dosing regimens. They also cannot be pooled, in part because of differences in reporting formats, but are individually reviewed in the Integrated Safety Summary.

The following table enumerates all subjects and patients across the entire development program.

Study ID	PI Location	Study Start Study Status	Design Control Type	Study and Control Drugs Dose, Route, and Regimen	No. of Subjects by Arm Entered/ Completed	Gender (M/F) Age Range (Years)	Diagnosis
Larger Phase II/III studies							
D-0007	Multi-center-USA	May 2001 complete	Phase III, randomized, open-label, Dacogen versus supportive care in adults with advanced-stage myelodysplastic syndrome	Dacogen IV 15mg/m^2 over 3- hr, t.i.d x 3d q6 weeks + Supportive Care Vs. Supportive Care Alone	89/83 81/81	59M/30F 31-85 57M/24F 30-82	MDS
PCH95-11	Multi-center-Europe	April 1996 complete	Phase II multi-center, single agent Dacogen in patients with myelodysplastic syndromes	IV 15 mg/m^2 over a 4-hr period, q8h, x3d, q 6 weeks	66/66	46M/20F 37-84	MDS
PCH97-39	Multi-center-Europe	August 1997 complete	Compassionate-use Dacogen in patients with myelodysplastic syndromes	IV 15 mg/m^2 over a 4- hr period, q8h, x3d, q 6 weeks	98/98	72M/26F 51-87	MDS
Older Phase I/II Studies							
PCH 88-01	Multi-center- Italy	1987 complete	Open-label, single-arm Phase I-II single-agent Dacogen in patients with AML and MDS (untreated or unresponsive to conventional treatment)	AML: starting at 30 changed to 60 escalating to 120 mg/m^2 over 4-hr t.i.d x3d, q 4 weeks MDS: starting at 15 escalating to 60 mg/m^2 t.i.d over 4-hr t.i.d x3d, q 4 weeks	38/38 (25 AML, 8 MDS, 5 CML	17M/21F 53-83	AML/MDS/CML

Demographics

Demographics are described above under the randomized controlled Phase III trial and the two Phase II trials.

Extent of exposure (dose/duration)

Dose. Each DAC cycle treatment cycle consisted of nine 15 mg/m^2 IV infusions. Patient compliance with dosing was determined by dividing the number of cycles in which all 9 infusions were administered by the total number of cycles given. In D-0007 trial, 86 patients exposed to DAC received 97% of their prescribed doses. Patient exposure is shown in Sponsor's Table 25 below.

Sponsor's Table 25. Patient Exposure to Study Drug*

Average Dose Per Treatment Cycle	Median Cumulative Dose Received in Study	Range of Cumulative Doses Received in Study
247 mg	735 mg	203-2614 mg

*Includes data from the 83 patients randomized to DAC and 3 patients randomized to SC who crossed over to receive DAC as delayed treatment.

Duration of Exposure. The median number of cycles completed was 3 for both the DAC and for the SC treatment arms, and the median number of months was 5.1 and 3.5 months in the DAC and the SC arms, respectively. In PCH 95-11 all 66 patients were exposed to DAC and received at least one course; 51 patients received at least 2 courses. In PCH 97-19, all 98 patients received at least one complete course; 73 patients received at least 2 courses.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

1. Data from the previous holder of the IND are included in this submission.
2. There are no post-marketing data, as the drug has not been marketed in any country.
3. Literature reports

Other studies

There were no other studies.

Postmarketing experience

There is no postmarketing experience, as DAC is not licensed in any country.

Literature

There is considerable current interest in DAC, since the description of a new mechanism of action, i.e. inhibition of DNA methylation during DNA synthesis and the relationship of DNA hypermethylation in a variety of neoplasms.

There have been a large number of reviews of the mechanism of action and of completed and on-going clinical studies. Among them should be mentioned the following:

- Myelodysplastic Syndromes at www.cancer.gov
- Mufti G, List AF, Gore SD, Ho AYL. Myelodysplastic Syndrome. Hematology (Am Soc Hematol Educ Program) 2003;:176-99.
- Greenberg PL, Young NS, Gatterman N. Myelodysplastic Syndrome. Hematology (Am Soc Hematol Educ Program) 2—2;:136-61.
- Jones PA. Effects of 5-azacytidine and its 2'-deoxyderivatives on cell differentiation and DNA methylation. Pharmacol Ther. 1985;(28):17-27.
- Hennessy BT, Garcia-Maner G, Kantarjian HM, Giles FJ. DNA methylation in hematological malignancies: the role of decitabine. Expert Opin Invest Drugs. 2003;12:1985-93.
- Issa JP. Decitabine. Curr Opin Oncol. 2003;15:446-51.
- Daskalakis M, Nguyen TT, Nguyen C et al. Demethylation of hypermethylated *P15/INK4B* gene in patients with myelodysplastic syndrome by decitabine treatment. Blood. 2002;100:2957-64.
- Hoffman WK, Koeffler HP. Differentiation therapy for myelodysplastic syndrome. Clin Cancer Res 2002;8:939-41.
- Silverman R. Targeting hypomethylation of DNA to achieve cellular differentiation in myelodysplastic syndromes (MDS). Oncologist. 2001;6:8-14.
- Lubbert M, Wijermans P, Kunzman R et al. Cytogenetic responses in high-risk myelodyspastic syndrome following low dose treatment with the DNA methylation inhibitor 5-aza-2'-deoxycytidine. Brit J Hematol. 2001;114:349-57.
- Wijermans P, Lubbert M, Verhoef G et al. Low-dose 5-aza-2'-deoxycytidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: a multicenter Phase II study in elderly patients. J Clin Oncol. 2000;18:956-62.
- Wijermans PW, Krulder JW, Huigens PC, Neve P. continuous infusion of low-dose 5-Aza-2'-deoxycytidine in elderly patients with high-risk myelodysplastic syndrome. Leukemia. 1997;11:S19-23.
- Kantarjian HM, O'Brien SM, Keating M et al. Results of decitabine therapy in the accelerated and blastic phases of chronic myelogenous leukemia. Leukemia. 1997:11:1617-20.

7.2.3 Adequacy of Overall Clinical Experience

- Three studies were submitted in this NDA, one controlled by best supportive care arm, the other two single-arm studies. In all, 240 patients were exposed to DAC in these studies. In addition, a multi-center Phase I/II study enrolled 38 patients, who received

higher doses of DAC than the MDS patients. An EORTC trial of 220 patients randomized to decitabine or placebo is underway. Altogether, this number of patients should provide adequate safety data.

- There are adequate numbers of male and female patients (in about 2:1 ratio, which is characteristic for MDS).
- There is inadequate racial or ethnic representation, as most of the study subjects were White (Caucasian).
- Doses and durations of DAC in the three studies submitted in this NDA are the same as proposed in the submitted package insert.
- One best supportive care-controlled randomized study of adequate size supported by two single-arm studies with similar results is sufficient to answer critical questions.
- There is only one approved drug in this drug class, the ribonucleotide analog, azacitidine. The toxicity profiles of the two drugs are very similar, if not identical. Both drugs act on replicating cells, inhibit DNA methylation at CG islands, induce cell differentiation and result in cell cytotoxicity. They have no P450 isozyme interaction, are mainly excreted in bile, but show little hepatotoxicity except in hepatically impaired patients, and little evidence of renal toxicity in absence of cardiac failure and dehydration.
- The following exclusionary criteria that were used in the trials also are valid for the use of decitabine in practice as the drug may pose additional dangers: autoimmune anemia, thrombocytopenia, active infection, neutropenia, HIV, uncontrolled cardiac disease, mental illness or other conditions preventing full cooperation.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Toxicology studies were adequately performed. Human pharmacology studies were difficult to perform due to the lack of a reliable assay (three were tried with varying success). Routine PK studies have been adequately performed. However, the relationship of PK to drug activity is uncertain. A pharmacodynamic assay is in development (i.e. the inhibition of DNA methylation).

7.2.5 Adequacy of Routine Clinical Testing

Study protocols were clearly described and followed. Any omissions were noted under Protocol Violations.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Section 5.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This drug was synthesized over 40 years ago, used in clinical trials for over 25 years, and subsequently developed under the auspices of NCI and two successive commercial sponsors.

7.2.8 Assessment of Quality and Completeness of Data

The safety data for DAC in the randomized D-0007 trial were of good quality and well presented. The data for the older Phase II studies show differences from the D-0007 data that are difficult to explain and may be less complete. The D-0007 data are similar to the data for azacitidine and more likely represent the adverse event profile for DAC.

7.2.9 Additional Submissions, Including Safety Update

The sponsor submitted a Safety Update on March 1, 2005 with data from new trials in MDS (ID03-0180) and AML (DAC-011). The safety profile in these studies is similar to what was reported in the original submission.

- No new conclusions regarding safety are warranted as a result of the update.
- No evidence of cumulative toxicity was found.
- No patient deaths were attributable to DAC treatment in the D-0007 trial. However, 6 patients died from disease complications exacerbated by myelosuppression that was treatment-related. Since the database lock for D-0007, 6 additional patients died; three from disease progression, one from AML, one from complications of AML, one from unknown cause.
- In the ongoing DAC-011 (AML) trial, 15 patients received DAC. Three died, one from progressive AML, one from intracerebral hemorrhage due to thrombocytopenia, one from retroperitoneal hemorrhage/cardiac arrest. Six additional patients in this trial died more than 30 days after the last study treatment, five from progression of AML, one from acute MI.
- Two unusual events occurred in a Phase I study of DAC in combination with valproic acid in selected hematologic malignancies. One patient with COPD died from fungal pneumonia, hyperammonemia, and progressive neurologic deterioration. (Hyperammonemia has not been previously reported). The other patient had worsening hypoxia and possible "differentiation [retinoic acid] syndrome" that resulted in death.
- The sponsor updated safety information using the literature search service Nerac, which discovered case reports and small studies of DAC in AML and CML, prior to initiating a phase III trial of DAC in patients with sickle cell anemia patients.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

- Virtually all patients treated with DAC reported adverse events, more than patients in the control arm.
- Most common adverse events were hematologic, especially thrombocytopenia, febrile neutropenia, leukopenia, and anemia.

- Likewise common were gastrointestinal disorders, such as nausea, vomiting, constipation, diarrhea, abdominal pain, stomatitis, dyspepsia and ascites.
- Infections were common, probably related to leukopenia, and included pneumonia, catheter infections, skin infections, and fungal infections.
- Fever, lethargy, peripheral edema, a variety of pains, headaches, hypesthesias, dizziness, insomnia, and confusion occurred more commonly in the DAC group than in the control group.
- Ecchymoses, patechiae, pallor, rashes, erythemas and other skin disorders were more common in the DAC group than in the control group.
- Hepatic enzyme elevations and renal function abnormalities were rare and their relationship to DAC uncertain.
- There were no drug-related deaths.
- SAEs were related to the MDS and mechanism of action of the drug resulting in neutropenia and infection, anemia and cardiovascular complications, thrombocytopenia and hemorrhage.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The adverse events tables for controlled study D-0007 and the Phase II studies are pooled above. The incidence of many adverse events appear to be similar, but hematological adverse events are unexplainably less frequent in the Phase II studies.

Pooled data vs. individual study data

As above.

Combining data

As above.

7.4.2 Explorations for Predictive Factors

Explorations for dose dependency for adverse findings. There was a standard dose administered to all patients with dose reductions and dose delays for neutropenia and thrombocytopenia.

Explorations for time dependency for adverse findings. The length of courses was the same, and the average number of courses administered was 2-3. Therefore time dependency could not be studied.

Explorations for drug-demographic interactions. The issue of greater percentages of responses in females than males was described above.

Explorations for drug-disease interactions. As described above, the adverse event profile of DAC is similar to the pathophysiology of MDS, therefore similar adverse events may be due to DAC or to MDS. It is clearly evident that hematological pancytopenias due to MDS worsen with DAC treatment until a response ensues.

Explorations for drug-drug interactions. Formal drug interaction studies have not been conducted. Patients in the clinical trials received various concomitant medications; no clinically significant interactions were noted. Possible potentiation by tamoxifen in causing severe thrombocytopenia (40,000/mm^3) with subsequent intracerebral bleeding occurred in one case.

7.4.3 Causality Determination. Since the pathophysiology of MDS results in similar adverse events as DAC, the sponsor chose to use a numerical difference between DAC-treated patients and supportive care patients experiencing a particular event to determine causality.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing schedule used in the three studies described in this NDA, which resulted in similar efficacy and safety, lends confidence to this dosage regimen. In the controlled study, DAC arm patients received 97% of prescribed doses.

- Thus, the starting dose of 15 mg/m^2 infused i.v. over 3 hours every 8 hours for three days every six weeks is an appropriate starting dose.
- Dose modifications depended on adverse events or lack of efficacy.
- There were no dose modifications for patients with hepatic or renal impairment, as these patients were excluded from the studies.
- Effect of food was not specifically investigated, since the drug is administered i.v.

The regimen can be improved in the following areas:

- The drug would be easier to administered if it could be administered subcutaneously rather than intravenously, or intravenously once daily over a shorter period of time. These studies are being carried out either by the sponsor or by academic investigators. The most promising regimen appears to be 20 mg/m^2 infused i.v. over 1-hour once daily for 5 days every 4 weeks. This regimen appears to be at least as effective and safe as the above regimen; however, only relatively few patients been so treated, making this conclusion premature.
- Appropriate dose modifications should be explored for patients with mild to moderate hepatic or renal impairment.

8.2 Drug-Drug Interactions

The use of concomitant medications paralleled the pattern of adverse events observed. For that reason, concomitant medications were used far more frequently in the DAC group. Possible potentiation by tamoxifen in causing severe thrombocytopenia (40,000/mm^3) with subsequent intracerebral bleeding occurred in one case.

8.3 Special Populations

Race. As noted above, the few non-White patients (4% African Americans, 2% from other origins) precluded analysis by race. About 93% of patients were White in the D-0007 trial. In the Phase II trials from Netherlands, Belgium and Germany most patients were presumed White, but racial background was not always entered in CRFs.

Gender. The following table (Sponsor's Table 30) will present the analysis by gender. In summary,

- Males in the DAC arm reported the following adverse events more frequently than women : neutropenia, thrombocytopenia, anemia, abdominal pain, fever, asthenia, hyperbilirubinemia, pneumonia, cellulitis, staphylococcal infections, hyponatremia, erythema, splenomegaly, dyspnea, sweating and
- Females in the DAC arm reported the following adverse events more frequently than men: febrile neutropenia, nausea, constipation, loose stools, stomatitis, headache, crackles in the lung, ecchymosis, pruritis and patechiae.
- Males in the SC arm reported the following adverse events more frequently than women: febrile neutropenia, splenomegaly, cardiac disorders, constipation, fever, pneumonia, cellulites, nervous system and psychiatric disorders, cough, dyspnea, ecchymosis, erythema, hyperhidrosis, and patechiae.
- Females in the SC arm had the fewest adverse events. The only one in which they surpassed men was headache.

Reviewer's Note: Neither the sponsor nor the reviewer performed statistical analyses of the significance of these differences between genders in patients with adverse events. The numbers of events were probably too small to draw conclusions. Nevertheless, at least a doubling of patients with adverse events (male vs. female) in a background where these adverse events are low in the SC arm suggest the following as possibly reflecting significant differences between genders:

- *In males, splenomegaly, abdominal pain, hyperbilirubinemia, pneumonia, and erythema.*
- *In females, febrile neutropenia, and stomatitis.*

Table 30 Adverse Events by Gender

SOC and Preferred Term	Dacogen N = 83 (%)		Supportive Care N = 81 (%)	
	Male (N = 55)	Female (N = 28)	Male (N = 57)	Female (N = 24)
Blood and lymphatic system disorders	55 (100)	25 (89)	49 (86)	20 (83)
Neutropenia	52 (95)	23 (82)	42 (74)	16 (67)
Thrombocytopenia	52 (95)	22 (79)	45 (79)	19 (79)
Anaemia NOS	49 (89)	19 (68)	42 (74)	18 (75)
Febrile neutropenia	12 (22)	12 (43)	5 (9)	0 (0)
Splenomegaly	6 (11)	0 (0)	7 (12)	0 (0)
Cardiac disorders	**18 (33)**	**9 (32)**	**14 (25)**	**3 (13)**
Eye disorders	**14 (25)**	**6 (21)**	**7 (12)**	**4 (17)**
Gastrointestinal disorders	**46 (84)**	**25 (89)**	**32 (56)**	**13 (54)**
Nausea	20 (36)	15 (54)	9 (16)	4 (17)
Constipation	16 (29)	13 (46)	9 (16)	2 (8)
Abdominal pain NOS	10 (18)	2 (7)	3 (5)	2 (8)
Loose stools	2 (4)	4 (14)	2 (4)	1 (4)
Stomatitis	2 (4)	8 (29)	3 (5)	2 (8)
General disorders and administrative site conditions	**48 (87)**	**24 (86)**	**49 (86)**	**16 (67)**
Pyrexia	32 (58)	12 (43)	17 (30)	6 (25)
Asthenia	15 (27)	4 (14)	15 (26)	6 (25)
Hepatobiliary disorders	**17 (31)**	**5 (18)**	**15 (26)**	**2 (8)**
Hyperbilirubinaemia	10 (18)	2 (7)	3 (5)	1 (4)

SOC and Preferred Term	Dacogen N = 83 (%)		Supportive Care N = 81 (%)	
	Male (N = 55)	Female (N = 28)	Male (N = 57)	Female (N = 24)
Infections and Infestations	**43 (78)**	**17 (61)**	**32 (56)**	**11 (46)**
Pneumonia NOS	15 (27)	3 (11)	9 (16)	2 (8)
Cellulitis	10 (18)	0 (0)	5 (9)	1 (4)
Staphylococcal infection	6 (11)	0 (0)	0 (0)	0 (0)
Investigations	**40 (73)**	**19 (68)**	**30 (53)**	**8 (33)**
Metabolism and nutrition disorders	**44 (80)**	**21 (75)**	**37 (65)**	**12 (50)**
Hyponatraemia	13 (24)	3 (11)	9 (16)	4 (17)
Musculoskeletal and connective tissue disorder	**31 (56)**	**20 (71)**	**24 (42)**	**9 (38)**
Nervous system disorders	**29 (53)**	**17 (61)**	**20 (35)**	**6 (25)**
Headache	13 (24)	10 (36)	7 (12)	4 (17)
Psychiatric disorders	**24 (44)**	**12 (43)**	**20 (35)**	**6 (25)**
Respiratory, thoracic and Mediastinal disorders	**45 (82)**	**20 (71)**	**42 (74)**	**10 (42)**
Cough	24 (44)	9 (32)	21 (37)	4 (17)
Dyspnoea NOS	17 (31)	6 (21)	20 (35)	5 (21)
Skin and subcutaneous tissue disorders	**46 (84)**	**22 (79)**	**39 (68)**	**8 (33)**
Ecchymosis	10 (18)	8 (29)	11 (19)	1 (4)
Erythema	10 (18)	2 (7)	4 (7)	1 (4)
Sweating increased	6 (11)	0 (0)	7 (12)	0 (0)
Pruritis	4 (7)	5 (18)	1 (2)	1 (4)
Vascular disorders	**30 (55)**	**21 (75)**	**23 (40)**	**7 (29)**
Petechiae	15 (27)	17 (61)	11 (19)	2 (8)

Source: Table 14.3.1.8 Summary of Adverse Events – Female Patients; Table 14.3.1.9 Summary of Adverse Events—Male Patients; Appendix 16.2.7.4 Listing of Adverse Events – Female Patients; Appendix 16.2.7.5 Listing of Adverse Events – Male Patients

Subgroup Analysis by Age. In both DAC and SC arms the largest groups of patients were aged 65-74 years. This group appears to have a greater number of adverse events than either the younger patients (<65 years of age) or the 75 years and older patients.

- There were very few adverse events in the DAC group that showed a trend, i.e. increasing with age or decreasing with age. Nausea, vomiting, constipation, and musculoskeletal

disorders decreased with age. Pallor increased with age. Most adverse events did not show a pattern.

- Most of the adverse events were reported at far greater frequency in the DAC arm than in the SC arm across all age groups. The following were more frequent in the DAC arm:
  - Gastrointestinal events,
  - Infections of all types,
  - Electrolyte disturbances possibly due to vomiting, diarrhea and dehydration,
  - Rare confusional states.
- Some adverse events were more frequent in the DAC arm and others in the SC arm among different age groups (such as leukocytosis, hypertension, elevation of liver function tests, hypocalcemia, headaches).
- Hematological abnormalities were reported almost as frequently in both arms, because this is a characteristic of MDS.
- Asthenia was uniformly more common in the SC arm in all age groups.
- In conclusion, analysis by age groups did not reveal any trends or dosing recommendations.

Table 31 Adverse Events by Age (< 65; 65–74 and ≥ 75)

SOC and Preferred Term	Dacogen N = 83 (%)			Supportive Care N = 81 (%)		
	< 65 y N = 22	65–74 y N = 40	≥ 75 y N = 21	< 65 y N = 30	65–74 y N = 35	≥ 75 y N = 16
Blood and lymphatic system disorders	21 (95)	39 (98)	20 (95)	27 (90)	31 (89)	11 (69)
Anaemia NOS	16 (73)	34 (85)	18 (86)	21 (70)	30 (86)	9 (56)
Splenomegaly	3 (14)	3 (8)	0 (0)	2 (7)	4 (11)	1 (6)
Leukocytosis	1 (5)	4 (10)	4 (19)	6 (20)	4 (11)	1 (6)
Cardiac disorders	**5 (23)**	**16 (40)**	**6 (29)**	**6 (20)**	**8 (23)**	**3 (19)**
Cardiac failure congestive	0 (0)	0 (0)	2 (10)	0 (0)	1 (3)	0 (0)
Ear and labyrinth disorders	**2 (9)**	**7 (18)**	**3 (14)**	**4 (13)**	**2 (6)**	**1 (6)**
Tinnitus	0 (0)	1 (3)	2 (10)	1 (3)	0 (0)	1 (6)
Eye disorders	**6 (27)**	**9 (23)**	**5 (24)**	**5 (17)**	**4 (11)**	**2 (13)**

SOC and Preferred Term	Dacogen N = 83 (%)			Supportive Care N = 81 (%)		
	< 65 y N = 22	65–74 y N = 40	≥ 75 y N = 21	< 65 y N = 30	65–74 y N = 35	≥ 75 y N = 16
Gastrointestinal disorders	**19 (86)**	**35 (88)**	**17 (81)**	**17 (57)**	**18 (51)**	**10 (63)**
Nausea	14 (64)	17 (43)	4 (19)	5 (17)	4 (11)	4 (25)
Constipation	9 (41)	14 (35)	6 (29)	1 (3)	5 (14)	5 (31)
Vomiting NOS	8 (36)	9 (23)	4 (19)	3 (10)	3 (9)	1 (6)
Abdominal pain NOS	4 (18)	7 (18)	1 (5)	3 (10)	2 (6)	0 (0)
Ascites	4 (18)	3 (8)	1 (5)	0 (0)	1 (3)	1 (6)
Dyspepsia	2 (9)	4 (10)	4 (19)	0 (0)	1 (3)	0 (0)
Glossodynia	0 (0)	2 (5)	2 (10)	0 (0)	0 (0)	0 (0)
Oral pain	0 (0)	1 (3)	2 (10)	1 (3)	0 (0)	1 (6)
Retching	0 (0)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)
General disorders and administrative site conditions	**20 (91)**	**36 (90)**	**16 (76)**	**27 (90)**	**28 (80)**	**10 (63)**
Fatigue	14 (64)	21 (53)	5 (24)	17 (57)	15 (43)	7 (44)
Asthenia	4 (18)	9 (23)	6 (29)	8 (27)	11 (31)	2 (13)
Catheter site haematoma	0 (0)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)
Catheter site haemorrhage	0 (0)	1 (3)	2 (10)	0 (0)	0 (0)	1 (6)
Injection site swelling	0 (0)	2 (5)	2 (10)	0 (0)	0 (0)	0 (0)
Hepatobiliary disorders	**4 (18)**	**12 (30)**	**6 (29)**	**6 (20)**	**10 (29)**	**1 (6)**
Infections and Infestations	**17 (77)**	**31 (78)**	**12 (57)**	**18 (60)**	**18 (51)**	**7 (44)**
Cellulitis	4 (18)	5 (13)	1 (5)	3 (10)	2 (6)	1 (6)
Staphylococcal infection	4 (18)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection NOS	3 (14)	2 (5)	0 (0)	3 (10)	4 (11)	0 (0)
Catheter related infection	0 (0)	2 (5)	5 (24)	0 (0)	0 (0)	0 (0)

SOC and Preferred Term	Dacogen N = 83 (%)			Supportive Care N = 81 (%)		
	< 65 y N = 22	65–74 y N = 40	≥ 75 y N = 21	< 65 y N = 30	65–74 y N = 35	≥ 75 y N = 16
Injury, poisoning and procedural complications	**4 (18)**	**13 (33)**	**3 (14)**	**5 (17)**	**5 (14)**	**2 (13)**
Investigations	**14 (64)**	**29 (73)**	**16 (76)**	**14 (47)**	**19 (54)**	**5 (31)**
Alanine aminotransferase increased	6 (27)	3 (8)	1 (5)	4 (13)	4 (11)	2 (13)
Blood alkaline phosphatase NOS increased	4 (18)	4 (10)	1 (5)	4 (13)	1 (3)	2 (13)
Blood creatinine increased	0 (0)	1 (3)	2 (10)	1 (3)	3 (9)	1 (6)
Blood carbon dioxide increased	0 (0)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)
Heart rate irregular	0 (0)	1 (3)	2 (10)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders	**16 (73)**	**32 (80)**	**17 (81)**	**16 (53)**	**24 (69)**	**9 (56)**
Hypocalcaemia	8 (36)	9 (23)	4 (19)	6 (20)	11 (31)	3 (19)
Hypokalaemia	6 (27)	9 (23)	3 (14)	2 (7)	5 (14)	3 (19)
Hypoglycaemia NOS	3 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	**15 (68)**	**27 (68)**	**9 (43)**	**10 (33)**	**14 (40)**	**9 (56)**
Pain in limb	8 (36)	7 (18)	1 (5)	2 (7)	3 (9)	3 (19)
Chest wall pain	3 (14)	3 (8)	0 (0)	1 (3)	0 (0)	0 (0)
Musculoskeletal discomfort	3 (14)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	**15 (68)**	**22 (55)**	**9 (43)**	**8 (27)**	**13 (37)**	**5 (31)**
Headache	10 (45)	12 (30)	1 (5)	2 (7)	5 (14)	4 (25)
Hypoaesthesia	4 (18)	5 (13)	0 (0)	0 (0)	1 (3)	0 (0)
Intracranial haemorrhage NOS	0 (0)	1 (3)	2 (10)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	**13 (59)**	**12 (30)**	**11 (52)**	**11 (37)**	**11 (31)**	**4 (25)**
Anxiety	4 (18)	4 (10)	1 (5)	4 (13)	4 (11)	0 (0)

SOC and Preferred Term	Dacogen N = 83 (%)			Supportive Care N = 81 (%)		
	< 65 y N = 22	65–74 y N = 40	≥ 75 y N = 21	< 65 y N = 30	65–74 y N = 35	≥ 75 y N = 16
Depression	4 (18)	4 (10)	1 (5)	5 (17)	6 (17)	0 (0)
Confusional state	2 (9)	4 (10)	4 (19)	0 (0)	1 (3)	2 (13)
Respiratory, thoracic and mediastinal disorders	**18 (82)**	**31 (78)**	**16 (76)**	**19 (63)**	**24 (69)**	**9 (56)**
Nasal congestion	4 (18)	1 (3)	0 (0)	3 (10)	2 (6)	2 (13)
Renal and urinary disorders	**4 (18)**	**11 (28)**	**6 (29)**	**4 (13)**	**6 (17)**	**4 (25)**
Micturition disorder	0 (0)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	**17 (77)**	**35 (88)**	**16 (76)**	**16 (53)**	**25 (71)**	**6 (38)**
Contusion	4 (18)	10 (25)	6 (29)	8 (27)	11 (31)	1 (6)
Ecchymosis	2 (9)	10 (25)	6 (29)	2 (7)	7 (20)	3 (19)
Vascular disorders	**13 (59)**	**25 (63)**	**13 (62)**	**12 (40)**	**14 (40)**	**4 (25)**
Pallor	3 (14)	10 (25)	6 (29)	5 (17)	4 (11)	1 (6)
Hypertension NOS	0 (0)	1 (3)	3 (14)	2 (7)	5 (14)	1 (6)
Haematoma NOS	0 (0)	2 (5)	2 (10)	0 (0)	2 (6)	1 (6)

Source: Table 14.3.1.10 Summary of Adverse Events—Patients Under 65 Years of Age; Table 14.3.1.11 Summary of Adverse Events—Patients 65–74 Years of Age; Table 14.3.1.12 Summary of Adverse Events—Patients 75 Years and Older; Appendix 16.2.7.6 Listing of Adverse Events—Patients Under 65 Years of Age; Appendix 16.2.7.7 Listing of Adverse Events—Patients 65–74 Years of Age; Appendix 16.2.7.8 Listing of Adverse Events—Patients 75 Years or Older

- The above analyses of adverse events suggest that special dosing considerations are not needed for gender or age.
- No statement can be made with regard to race.
- Pediatric population, patients with hepatic or renal insufficiency, and pregnant or lactating women were excluded from these studies.

8.4 Pediatrics

MDS is rarely seen in the pediatric age group.

8.5 Advisory Committee Meeting

There are no plans to present this application to the Oncology Drugs Advisory Committee.

8.6 Literature Review

Literature references are cited throughout, under 7.2.2.3, and under References at the end of the review. A formal review was not carried out, as plentiful high quality reviews are widely available, cancer.gov review being a prominent example.

8.7 Postmarketing Risk Management Plan

There is an on-going EORTC trial in which MDS patients have been randomized to decitabine or best supportive care, and the primary endpoint is overall survival.

8.8 Other Relevant Materials

Division of Drug Marketing, Advertising and Communication agreed with the sponsor's proposed name of DACOGEN.

9.0 OVERALL ASSESSMENT

9.1 Conclusions (also see 4.3 Data Quality and Integrity)

1. DAC is an agent that reduces the hypermethylation of DNA, which is common in MDS. Decreased hypermethylation (or hypomethylation) of DNA is thought to result in restoration of normal growth control in hematopoietic cells. As a result, a response to DAC results in complete or partial normalization of blood counts and bone marrow blast percentages (where previously abnormal), and patients are no longer dependent on transfusion of RBCs and/or platelets. Elimination of transfusion dependence results in decreased discomforts and decreased risks of transfusion hemosiderosis, transfusion reactions, and possible infections. DAC treatment has not been shown to decrease the risk of development of AML or to increase overall survival.
2. The data in this submission demonstrate that a minority of MDS patients (about 17%-26% in the ITT populations of the three studies) had long-lasting complete or partial responses to DAC. In the controlled trial, 17% of patients in the DAC treatment arm had a response, while none of the patients in the supportive care arm had a response. This difference in response rates between the two arms was highly significant ($p < 0.001$).
3. The response rates were higher in those patients who were able to complete at least two cycles of therapy, the minimum required for a response. Among these patients, the response rates were about 21% to 40% in the three studies (the wide range in response rates between studies may have been due to differences in definitions of responses).

4. The responses were long-lasting. Median ranges for the three studies were 146, 250, and 266 days in the three studies.
5. Thus, decitabine is useful for eliminating transfusion dependence in patients with complete and partial responses and also in Hematological Improvement patients (whose responses failed to meet the criteria for partial response). Between these response categories, 28% to 41% of DAC-treated patients lost the need for transfusions.
6. Subgroup analyses showed that responses to DAC occurred at similar frequencies in all FAB classification subtypes, in High-risk, INT-2 and INT-1 IPSS subtypes, in all age ranges, in both genders, in patients with prior therapy for MDS and in patients without prior therapy, and in *de novo* MDS and secondary MDS. IPSS prognostic group did not predict the probability of response.
7. Major and minor cytogenetic responses occurred in about one-half of complete and partial responders.
8. Quality of life analyses showed improved global health status, dyspnea and fatigue in the DAC treated patient group but not in supportive care patient group.

9.2 Recommendation on Regulatory Action

The data presented in this NDA suggest that DAC is approvable for treatment of MDS patients with all FAB subtypes and High-risk, INT-2, and INT-1 IPSS subtypes, previously treated as well as untreated patients, and patients with *de novo* or secondary MDS. **However, because of the deficiencies noted in 4.3 Data Quality and Integrity, approval of DAC is contingent on submission by the sponsor of verifiable data supporting the efficacy and safety of DAC in MDS.**

DAC is an inhibitor of DNA methylation, promoting differentiation of hematopoietic cells, and is also a cytotoxic agent causing cell cycle arrest and apoptosis. It is effective in about 17% to 26% of MDS patients in completely or partially restoring normal blood cell counts and normal percentage of blasts in the bone marrow, and in reducing or eliminating transfusion dependence. The therapeutic effects are generally long lasting. DAC treatment has not been shown to result in survival benefit. The goals of decitabine treatment should be to restore normal blood cell counts and bone marrow blast percentages and to eliminate transfusion dependence.

The dose of decitabine is 15 mg/m^2 administered intravenously over 3 hours; this dose is repeated every 8 hours for 3 days every six weeks. The dose is adjusted according to blood cell counts. Patients should be treated for a minimum of four 6-week cycles.

Reviewer's recommendations for decitabine (Dacogen™) labeling are not incorporated into this review.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Postmarketing safety reports (21 CFR 314.80).

9.3.2 Required Phase 4 Commitments

As noted above, a controlled trial, in which MDS patients are randomized to DAC or placebo, is on-going under EORTC auspices.

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

The major changes will be in the description of the mechanism of action. Description of the Clinical Studies results is contingent on review of verified data.

The trade name was reviewed by Division of Medication Errors and Technical Support (DMETS); there are no issues with the proposed name.

A medication guide is not necessary, as DAC will be administered by health care professionals.

9.5 Comments to Applicant

The sponsor will be requested to submit a Data Verification Plan.

10. APPENDICES

10.0 Review of Individual Study Reports

Data included in the text of the review.

10.1 Line-by-Line Labeling Review

Labeling review will be performed at the time of resubmission of this NDA.

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/s/

Edvardas Kaminskas
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Division Director Summary Review of a New Drug Application

NDA: 21-970
Drug: Dacogen™ (decitabine) for Injection
Applicant: SuperGen, Inc.
Date: August 27, 2005

This new drug application was received on November 1, 2004 for the following proposed indication:

> Dacogen is indicated for treatment of patients with Myelodysplastic Syndrome including previously treated and untreated, *de novo* and secondary MDS of the following subtypes:
>
> FAB: refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.
>
> IPSS: High-risk, INT-2, and INT-1

The proposed dosing regimen is "15 mg/m^2 administered by continuous intravenous infusion over three hours repeated every 8 hours (q8h) for three days... This cycle should be repeated every six weeks. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles. Treatment may be continued as long as the patient continues to benefit."

Clinical Review

The Clinical Review was completed by Edvardas Kaminskas, M.D. on August 22, 2005. The following recommendation on regulatory action, required phase 4 commitment, summary of the clinical program, and efficacy and safety findings are excerpted from the Executive Summary of Dr. Kaminskas' review:

> 1.1 Recommendation on Regulatory Action
>
> Approval of decitabine for treatment of patients with myelodysplastic syndrome (MDS). **The data in this NDA were reviewed as submitted. As described below, these data suggest that decitabine is approvable for the stated indication. However, inspections of the two largest sites of subject enrollment by the Division of Scientific Investigations led to the conclusion that data collected by these two sites are unreliable (see below in 4.3 Data Quality and Integrity). Therefore, from a clinical perspective, approval of decitabine is contingent on the submission by the sponsor of verifiable data supporting the efficacy and safety of decitabine in MDS.**

1.2.2 Required Phase 4 Commitments

Completion of EORTC 06011 Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.

1.3.1 Brief Overview of Clinical Program

Product name, class, starting dose and route of administration: Dacogen™ for Injection contains decitabine, an analogue of the natural deoxyribonucleoside 2'-deoxycytidine. Decitabine promotes cell differentiation and is also cytotoxic. Dacogen is administered by a 3-hour intravenous infusion at a starting dose of 15 mg/m^2 every 8 hours for three days every 6 weeks.
Indications and populations studied: Adult patients with all FAB subtypes of myelodysplastic syndrome.
Number of pivotal efficacy and safety trials: One Phase III controlled trial, supported by two single-arm Phase II trials.
Number of patients enrolled in the primary trials: 170 in the Phase III trial and 164 in the Phase II trials.
Overall number of patients in the safety database and extent of exposure: 240 patients in the three primary studies and 183 patients in six ongoing studies. In the Phase III controlled trial, the average dose per treatment cycle was 247 mg, median number of cycles was 4, and the median cumulative dose received was 735 mg (range, 203-2614 mg).

1.3.2 Efficacy

Efficacy of decitabine in treatment of MDS is demonstrated in the controlled, randomized Phase III trial D-0007, in which of 89 patients randomized to decitabine 83 were treated with decitabine (plus 3 crossover patients from the supportive care arm) and 81 patients received supportive care only. Similar efficacy results were found in the two single arm, multicenter Phase II studies, PCH 95-11 and PCH 97-19, in which 66 patients and 98 patients, respectively, were treated with decitabine. All three trials had enrolled patients with MDS of all FAB subtypes and of high-risk, intermediate-2 and intermediate-1 IPSS categories.

Endpoints: There were two primary endpoints in the controlled trial, overall response rate (complete or partial) and time to progression to acute myeloid leukemia or death. Secondary endpoints included survival, transfusion requirements, overall response rate plus the rate of hematological improvement (a lesser than partial response), quality of life measures, and cytogenetic response. The primary endpoints in both Phase II studies were best hematological response (defined as complete remission, partial remission, improvement, stable disease,

relapse, or progression), transfusion requirements, and changes in performance status.

Endpoint issues:

- The sponsor initially proposed overall response rate as the primary endpoint for the controlled trial, while the Agency suggested time to progression to AML or death. Both became co-primary endpoints. The possibility of achieving a statistically significant delay in time to progression to AML or death with decitabine treatment was suggested by the CALGB 9221 trial in which MDS patients were treated with azacitidine, an agent with a similar mechanism of action. A later statistical analysis of this trial by the Agency concluded that such a delay was not demonstrated. Thus, there is so far no evidence that any agent is effective in prolonging the time to progression to AML or death in MDS patients.

- The definitions of overall response rates differ between the pivotal controlled trial and the Phase II studies, as criteria for response rates changed with publications by international working groups. The main difference is that a complete or partial response by the later criteria needs to be maintained for at least 8 weeks, while the earlier criteria have no such requirement.

Efficacy Conclusions:

(Please see Executive Summary 1.1. The conclusions below were based on data as submitted).

- Patients treated with decitabine had an overall response rate of about 17% (in ITT population) as compared to no responses in the supportive care patients. This difference was statistically significant ($p < 0.001$). Decitabine-treated patients in the single-arm studies had overall response rates of 24% and 26% (ITT populations).
- Time to progression to AML or death was not significantly different in decitabine-treated patients from that in supportive care patients ($p=0.160$).
- The clinical benefit of decitabine-induced responses was normalization of blood counts and bone marrow blast percentages and elimination of the need for transfusions in patients who were transfusion-dependent at baseline.
- The responses were long-lasting. The median durations of responses were 266 days, 146 days, and 250 days in the controlled trial D-0007, PCH 97-19 study, and PCH 95-11 study, respectively. The median time to response in the controlled trial was 89 days.
- Subgroup analyses revealed:
    - Patients with MDS of all FAB subtypes and IPSS classifications had approximately similar response rates.
    - Patients of all age ranges had similar response rates.
    - Female patients had twice the response rates of male patients in two of the studies, and about the same response rate as male patients in the third study. This reviewer, in light of similar response rates in female

and male MDS patients in the azacitidine trials, is not convinced that there is gender difference in response rate to decitabine.
    - Response rates were not analyzed by race/ethnicity, because more than 90% of the subjects were White.
    - Responses occurred in patients with or without prior therapy for MDS and in patients with *de novo* and with secondary MDS, although there were too few patients with secondary MDS or with prior therapy for MDS to make comparisons of response rates.
- Analyses of secondary endpoints revealed:
    - Decitabine treatment had no effect on overall survival.
    - Decitabine treatment resulted in decreased RBC and platelet transfusion requirements in transfusion-dependent patients, and decreased the risk of patients becoming transfusion-dependent.
    - Febrile neutropenia occurred more frequently in decitabine-treated patients than in supportive care patients.
    - Hematological Improvement rates (Complete Response plus Partial Response plus Hematological Improvement) were higher in decitabine-treated patients than in supportive group patients.
    - In Quality of Life analyses, decitabine-treated patients had statistically superior global health status, dyspnea and fatigue.
    - About 19% (9/48 patients with clonal abnormalities at baseline) had a major cytogenetic response (no abnormality) and 2% (1/48) had a minor cytogenetic response ($\geq$ 50% reduction in abnormal metaphases) in the decitabine treatment arm. About one-half (8/15) of patients who had a CR or PR had a major cytogenetic response. About 6% (2/33) of patients in the supportive care arm had a major cytogenetic response.

Dosage regimen is appropriate, since controlled trial patients received 97% of the prescribed dose. Delays of treatment and dose reductions in subsequent cycles occurred in about one-third of patients.

Role in armamentarium: The efficacy of decitabine in MDS is similar to that of azacitidine as measured by response rate.

1.3.3 Safety

(Please see Executive Summary 1.1. The conclusions below were based on data as submitted).

- A total of 240 patients with MDS received decitabine at the same dose as specified in the NDA in the three primary studies. Decitabine was administered in cycles of 6 weeks, and the median number of cycles was 3, with some patients receiving up to 9 cycles.
- There were no deaths that were attributed to DAC toxicity, although thrombocytopenia aggravated by DAC treatment may have contributed to bleeding, including intracerebral hemorrhage. The number of deaths was greater in the supportive care arm than in the DAC treatment arm during the

study period; however, the total number of deaths during the total observation period was about the same in both arms. Disease progression to AML and infection were the most common causes of death in both arms.

- Hematological adverse events (neutropenia, febrile neutropenia, thrombocytopenia, anemia and leukopenia) were prominently more common in the decitabine arm than in supportive care arm. Hematological adverse events did not decrease with successive cycles unless the patient had a response. Gastrointestinal disorders (nausea, constipation, diarrhea, vomiting, abdominal pain, stomatitis, dyspepsia and ascites) were more common in the decitabine arm than in the supportive care arm. They decreased after the first two cycles of decitabine therapy with appropriate medications. Fever, bacterial and fungal infections, painful joints or muscles, backaches, chest wall discomfort, headache, insomnia, confusional state, ecchymoses, pallor, erythemas, alopecias and skin disorders were also more common in the decitabine arm than in the supportive care arm. There were no greater than grade 2 hepatic or renal function abnormalities. Vital signs reflected general clinical condition rather than MDS or decitabine therapy.
- Adverse events (thrombocytopenia, lymphadenopathy, neutropenia, pneumonia, *M. avium* infection, cardiac arrest, and elevated liver function tests) led to discontinuation of decitabine therapy in 10% of patients, and of withdrawal from the supportive care arm in 2% of patients (because of COPD and of dyspnea). About 19% of patients had dose delays, about 5% of patients had dose reduction, and about 11% of patients had dose reduction and dose delay.
- There are no safety data on pregnant or lactating women (who were excluded from enrollment), or on infants and children (MDS is very rare in childhood) in this submission.
- Overdose data is available from older studies in which patients were treated with several-fold higher decitabine dosages. The main toxicity was hematological.
- The most common adverse events due to decitabine overlap those of MDS, making attribution and safety evaluation difficult. Decitabine therapy is effective in eliminating or reducing transfusion dependence, and the adverse events appear to be tolerable for the achievement of this goal.

Medical Team Leader's Review

The Medical Team Leader Review by Ann Farrell, M.D. was completed on August 25, 2005. The review summarized the safety and efficacy data from the clinical trials and the following results of the DSI inspection:

> The DSI audited the 2 sites that accrued the most patients to the major trial. These sites were: [redacted], and [redacted]. When the inspectors checked the source documentation with the case report forms (CRFs) and data listings (DL), they uncovered multiple instances where patients' data

were inconsistent. At the ———— , 34 patients were enrolled in the study. Of those 34 enrolled patients, 12 patient records were inspected. Of those 12 patient records, 6 (50%) had inconsistent data. For some patients, the source document said that the patient had a transfusion and the CRF or data listings did not and for other patients, the source documentation stated that the patient did not have a transfusion and the CRFs and data listings did. At the ———— ———— site, similar observations were found although the frequency appeared less. Since the primary endpoint encompassed data on transfusions and the demonstration of decitabine's proposed clinical benefit was the elimination of transfusions, the transfusion data appears too unreliable to be used for an approval decision.

Dr. Farrell's summary, conclusions and recommendations are quoted below:

> This reviewer recommends that the application not be approved because of the problems uncovered during the Division of Scientific Investigations (DSI) site inspections. The DSI inspections discovered that discrepancies between source documents, Case Report Forms (CRFs), and Data Listings concerning transfusions. Transfusion data is crucial for assessment of response as well as clinical benefit in this application. Therefore, the lack of reliability of the transfusion data for the main phase 3 trial renders the study results uninterpretable...
>
> As stated above, the transfusion data appears too unreliable to be used for an approval decision. This team leader recommends the following options:
>
> 1) The sponsor could recollect all transfusion data from source documentation and based on that data recollection submit an amendment to the current NDA revising the endpoints, study report/results, CRFs, data listings, and data sets as necessary. Following the resubmission, DSI would again inspect sites, possibly increasing the number of sites inspected.
> 2) The sponsor could submit the study report and results from the EORTC 06011 Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy when the study is completed.

Division of Scientific Investigations Clinical Inspection Summary

The Division of Scientific Inspections' Clinical Inspection Summary was completed on July 28, 2005. Two of the sites that accrued the most patients to study D-007 were inspected:

CI Name	City, State	Site Number	Inspection Date	Conducted under IND?	Classification
Hussain Saba, M.D.	Tampa, FL	1006	5/4-5/20/05	Yes	VAI
John DiPersio, M.D.	St. Louis, MO	1003	5/25-6/10/05	Yes	VAI

DSI's overall assessment of findings and general recommendations are provided below:

> Based on the observations described above, the data collected by Dr. Saba and DiPersio are unreliable. Transfusion documentation at both sites was inadequate and inaccurate. CBCs and bone marrow assessments, tests that monitor bone marrow response, were not performed as the protocol required. Five subjects at Dr. DiPersio's site were enrolled into the study but met exclusion criteria. Finally, the stability of some administered decitabine infusions is questionable because there is no documentation or the documentation indicates that the duration of the infusions was longer than decitabine's determined stability.

Statistical Review

The Statistical Review was completed by Kun He on July 29, 2005. The review focused on the randomized trial, study D-007. The summary and conclusions are quoted below:

> 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.

Clinical Pharmacology and Biopharmaceutics

The Clinical Pharmacology and Biopharmaceutics Review was completed by Roshni Ramchandani, Ph.D. on August 1, 2005. The review recommended changes to the CLINICAL PHARMACOLOGY and PRECAUTIONS sections of the package insert. In addition, the review recommended the following Phase 4 commitments:

1. We recommend that you conduct a mass balance study to assess renal and non-renal pathways of elimination of decitabine and we recommend that you screen any major metabolites in vitro for pharmacological activity to determine if there any need for any organ impairment studies.

Rationale: Very limited data is available on the pharmacokinetics of decitabine. The exact metabolic fate and pathways of elimination of decitabine are unknown. This information is critical in determining if decitabine can be used in patients with renal and/or hepatic impairment and if dosing adjustments would be needed for the safe use of decitabine in these patients.

2. We recommend that you conduct exposure-response analyses for measures of toxicity and effectiveness in ongoing and future clinical studies. You should consider assessing intracellular levels of drug and active metabolites as measures of exposure in the exposure-response analysis. These analyses may help enable the determination of optimal dosing regimens for MDS as well as for other indications.

Rationale: The optimal dosing regimen for decitabine in MDS is not known. Only one dosing regimen of decitabine was evaluated in the current submission. The exposure-response relationship for decitabine has not been elaborated. Characterization of the exposure-response relationship for decitabine can help in optimization of dosing regimens for MDS as well as for other future indications.

3. We suggest that you plan to evaluate the ex vivo DNA methyl transferase (DNMT) inhibition following decitabine, as a measure of its pharmacological activity, and if DNMT inhibition is correlated with exposure and with response rates in ongoing and future studies.

OR

We suggest that you plan to evaluate the ex vivo DNA methyl transferase (DNMT) inhibition following decitabine, as a measure of its pharmacological activity, and also evaluate if DNMT inhibition is a predictor of response to decitabine in ongoing and future studies.

Rationale: In vitro data indicates that decitabine inhibits DNMT, and studies have shown that hypomethylation of DNA restores expression of tumor suppressor genes and induces cell differentiation. Examination of the ex vivo DNMT inhibition in ongoing and future clinical studies of decitabine would be important in improving the understanding of the PK-PD relationship for decitabine. Further, understanding the correlation of exposure of decitabine and/or its active metabolites to DNMT inhibition and how that links to clinical response rates would be important in predicting exposures associated with optimal clinical response rates and might help to identify responders and non- responders to treatment.

4. We suggest that you explore the effect of cytidine deaminase polymorphisms on the exposure-response relationships for measures of effectiveness and toxicity, as part of ongoing and future studies of decitabine.

Rationale: Single nucleotide polymorphisms in the gene for cytidine deaminase (HDCA) have been shown to be associated with Ara-C (an analog of decitabine) toxicity in a Japanese study (Yue et al., 2003). In this study three different polymorphisms (A79C, G208A and T435C) were identified in the coding region of the HDCA gene and displayed allelic frequencies of 20.1%, 4.3% and 70.1%, respectively. One of the polymorphisms, G208A produced an alanine to threonine substitution (A70T) within the catalytic domain and showed that patients with the polymorphism showed greater sensitivity to Ara- C treatment than those without the polymorphism. The occurrence of these polymorphisms and their role in the exposure-response and exposure-toxicity relationships for decitabine needs to be evaluated to further optimize treatment strategies in patients.

Additional Recommendations for the Applicant:

1. We recommend that you conduct in vitro studies to determine the CYP450 inhibition and induction potential of decitabine. Depending on the results, drug-drug interaction studies may be necessary. We also recommend that you conduct in vitro studies to evaluate if decitabine is a substrate of p-glycoproteins and its inhibition potential for p-glycoproteins.

Pharmacology/Toxicology Review

The Pharmacology/Toxicology Review was completed by Anwar Goheer, Ph.D. on June 22, 2005. The review concluded that the "Product is approvable from pharmacology/toxicology point of view. There are no outstanding issues."

Chemistry, Manufacturing and Controls Review

The first CMC review by Dr. Josephine Jee was completed on July 14, 2005. The review recommended the following:

> This application is approvable from the standpoint of Chemistry, Manufacturing and Controls (CMC). A number of deficiencies related to the drug substance and drug product have been identified and conveyed to the applicant to address. In addition, pending microbiological issues are yet to be satisfactorily addressed.

The applicant has provided a response to these deficiencies which is under review. On August 26, 2005 the Chemistry Team Leader, Dr. Chidambaram, stated that the applicant has responded adequately to all of the deficiencies. However, he stated that there may be a new deficiency regarding the proposed method of inspection of the drug product for particulates. He expects the review to be finalized on August 29, 2005.

The facilities inspections (EER) were found to be acceptable.

Microbiology Review

The first Product Quality Microbiology Review by Janet Barletta, Ph.D., dated May 5, 2005, stated that the application was approvable pending revision. The deficiencies were communicated to the applicant. The applicant responded to the deficiencies on June 1 and 13, 2005. The second microbiology review of July 15, 2005, concluded that the responses were acceptable and recommended approval based on microbiological product quality.

Consultation from the Division of Medication Errors and Technical Support

The proprietary name review by DMETS/ODS was completed on June 22, 2005. DMETS had no objections to the use of the proprietary name, Dacogen, provided recommendations for label and labeling revisions, and found the name to be acceptable from a promotional perspective.

Consultation from the Division Drug Marketing, Advertisement, and Communications

On July 14, 2005, DDMAC provided a number of comments on the draft labeling for consideration during the labeling negotiations.

Conclusions and Recommendations

1. I concur that the DSI inspections have raised significant concerns about the quality of the data, particularly regarding the response and transfusion endpoints. Questions concerning the reliability of the data at both of the sites that were inspected suggest that the monitoring of the study may not have been adequate. The applicant needs to verify the data at all study sites and submit a report. Depending on the findings, the applicant may need to re-do the analyses and revise the study report. To ensure data integrity, DSI will need to re-inspect the [redacted] sites, and inspect several additional sites. Of the two possible actions (non approval vs. approvable), I concur that an approvable action is the most appropriate. The applicant verified the data at study D-0007 sites 1003 and 1006 and submitted a Data Verification Report dated August 24, 2005. While this report has not yet been reviewed, the report states that no objective responses had to be reclassified and that impact on response duration was minimal. In addition, the applicant is sponsoring study EORTC 06011, a Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy. If positive, the results of this study could be submitted in support of the application.

2. I concur with the clinical phase 4 commitment to submit the results of study EORTC 06011.
3. I concur with the Clinical Pharmacology and Biopharmaceutics phase 4 commitments.
4. The DMETS comments on the labeling do not appear to have been sent to the applicant. These should be communicated to the applicant but do not need to be included in the action letter.
5. Since the clinical results may change, labeling negotiations should be deferred until the applicant submits a complete response to the approvable letter.

{see appended electronic signature page}

Robert L. Justice, M.D., M.S.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Robert Justice
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MEDICAL OFFICER

Division of Oncology Drug Products

Medical Team Leader's Review

NDA:	21790
Sponsor:	SuperGen Pharmaceuticals
Drug Product:	Decitabine, Dacogen™
Projected Action Date:	August 29, 2005

Summary

On October 24, 2004, SuperGen Inc. submitted this New Drug Application (NDA) for decitabine, a new molecular entity, for the treatment of myelodysplastic syndrome (MDS) for approval. This application contains 2 open-label, single arm phase 2 studies in MDS and 1 randomized, multicenter, open-label phase 3 trial.

This reviewer recommends that the application not be approved because of the problems uncovered during the Division of Scientific Investigations (DSI) site inspections. The DSI inspections discovered that discrepancies between source documents, Case Report Forms (CRFs), and Data Listings concerning transfusions. Transfusion data is crucial for assessment of response as well as clinical benefit in this application. Therefore, the lack of reliability of the transfusion data for the main phase 3 trial renders the study results uninterpretable.

Background:

MDS

At the present time, myelodysplasia is an incurable and progressive disease with an estimated 15,000 – 20,000 new cases diagnosed each year in the US. The myelodysplastic syndromes (MDS), formerly called pre-leukemia or "smoldering" leukemia, consist of a group of heterogeneous diseases characterized by ineffective hematopoiesis leading to one or more peripheral cytopenias (neutropenia, anemia, thrombocytopenia) and progressive bone marrow failure. Although the disorder can be found in children as well as adults, the highest prevalence occurs in those over 60 years of age.

Treatment for MDS ranges from supportive care to bone marrow transplantation. Remissions do not occur without treatment. The only hope for a cure is an allogeneic bone marrow transplantation (AlloBMT). Few MDS patients are eligible for an AlloBMT because of the age limitation of this procedure (i.e., less than 65). Recently some older patients with MDS have been undergoing nonmyeloablative therapy. Most patients receive supportive care which may

include cytokine therapy (erythropoietin, granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor), red blood cell and platelet transfusions, and prophylactic antibiotics. The only approved therapy for MDS is Vidaza (azacitadine), a chemical entity similar in structure to decitabine. Patients whose disease responded to Vidaza experienced clinical benefit such as elimination of the need for red blood cell transfusions.

Regulatory History

SuperGen Inc. acquired decitabine from in 1999. Pharmachemie had started development of decitabine under IND 33929.

Since 2001, SuperGen has had several meetings with the division to discuss the major trial submitted for this application, d-0007. The major trial, d-0007 enrolled its first patient in July 2001 and completed enrollment in January 2004.

The division granted decitabine Fast Track status based on interim results from the first 45 patients.

On October 24, 2004, SuperGen Inc. filed the NDA.

For additional details, please see Dr. Kaminskas' review.

Chemistry:

Dacogen™ (decitabine) for Injection contains decitabine, an analogue of the natural nucleoside 2'-deoxycytidine. Decitabine is a fine, white, crystalline powder with the molecular weight of 228.21. Dacogen's chemical name is 4-amino-1-(2-deoxy-â-D-erythro-pentofuranosyl)- 1,3,5-triazin-2(1*H*)-one.

Dacogen™ for Injection is supplied as a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 mL, single dose, glass vial contains 50 mg decitabine, 68 mg Monobasic Potassium Phosphate (Potassium Dihydrogen Phosphate) and 11.6 mg Sodium Hydroxide.

For further details, please see Dr. Jee's Chemistry, Manufacturing, and Control review of this NDA.

Microbiology:

The microbiology reviewer, Dr. Barletta, recommends approval.

Nonclinical Pharmacology and Toxicology Information:

Mechanism of Action
Dacogen is an inhibitor of DNA methyltransferease enzymes. Decitabine is believed to also promote differentiation and apoptosis.

For further details, please see the Pharmacology and Toxicology reviews of this NDA.

Human Pharmacology:

The mean (±SD) maximum plasma concentration (Cmax) was 0.459 ± 0.100 µg/mL and mean area under the concentration-time curve (AUC0-□‡) was estimated to be 408±88 ng•h/mL. For the sponsor's study report, "In patients with advanced solid tumors after 72-hour infusions at 20 (n=7), 25 (n=6), or 30 (n=4) mg/m2/day AUC of decitabine was 543 ± 158, 743 ± 95.0, and 743 ± 124 ng h/mL, respectively."

Decitabine has a plasma protein binding which is negligible (<1%).

The major elimination of decitabine is by cytidine deaminase. *In vitro* testing has suggested that decitabine is not a substrate for human liver P450 enzymes. Urinary excretion of unchanged decitabien is less than 1% of the total dose.

The application lacked some information on the clinical pharmacology of decitabine. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) identified the following issues of concern:

The influence of age, gender, race and organ dysfunction on the pharmacokinetics of decitabine has not been evaluated. Potential interactions with drugs, which are substrates, inhibitors, or inducers of the cytochrome enzymes, have not been evaluated.

Office of Clinical Pharmacology and Biopharmaceutics Phase 4 Commitments

The following recommendations are from their review:

1. We recommend that you conduct a mass balance study to assess renal and non-renal pathways of elimination of decitabine and we recommend

that you screen any major metabolites in vitro for pharmacological activity to determine if there any need for any organ impairment studies.

2. We recommend that you conduct exposure-response analyses for measures of toxicity and effectiveness in ongoing and future clinical studies. You should consider assessing intracellular levels of drug and active metabolites as measures of exposure in the exposure-response analysis. These analyses may help enable the determination of optimal dosing regimens for MDS as well as for other indications.
3. We suggest that you plan to evaluate the *ex vivo* DNA methyl transferase (DNMT) inhibition following decitabine, as a measure of its pharmacological activity, and if DNMT inhibition is correlated with exposure and with response rates in ongoing and future studies.
4. 
5. We recommend that you conduct *in vitro* studies to determine CYP450 inhibition.

Clinical Studies Summary:

The tables below show the studies submitted for review. All studies were open-label. The studies below which are bolded are the main ones reviewed in this application.

Table of Decitabine Studies (Adult)

Study Identifier	Study Design	Objectives	Patient Population	Dose escalation range and regimen
PCH- 88-01	Multicenter, single agent, dose ranging	Dose determination for AML and MDS	Untreated or refractory patients with 25 AML or 8 MDS (also enrolled CML)	AML 30-170mg/m^2 over 4 hrs thrice daily for 3 days, every 4 weeks MDS 15-60mg/m^2 over 4hrs thrice daily for 3 days, every 4 weeks
PCH 91-01	Multicenter, single agent	Response rate	21 MDS patients	Continuous infusion 500mg/m^2/d for 3 days, every 5-6 weeks
PCH 91-02	Multicenter, single agent	Response rate	48 MDS patients	Continuous infusion 500mg/m^2/d for 3 days, every 5-6 weeks
PCH 95-04	Single center, single agent	Compassionate use	8 MDS patients	Continuous infusion 500mg/m^2/d for 3 days, every 5-6 weeks
PCH 95-05	Single center, single agent	Response rate	14 MDS patients	MDS 15 mg/m^2 over 4 hrs thrice daily for 3 days, every

				28 days
PCH 95-11	Multicenter, single agent	Response rate	66 MDS patients	MDS 15 mg/m^2 over 4 hrs thrice daily for 3 days, every 6 weeks
PCH 97-19	Multicenter, single agent	Compassionate use	98 MDS patients	MDS 15 mg/m^2 over 4 hrs thrice daily for 3 days, every 6 weeks
D-0007	Multicenter, randomized, controlled trial	Response rate comparison with supportive care	MDS patients	MDS 15 mg/m^2 over 3 hrs thrice daily for 3 days, every 6 weeks

Reviewer's Table

There are other completed studies of the use of decitabine in pediatric malignancy. These studies were not submitted and are not the focus of the application.

The sponsor also has an ongoing EORTC study, EORTC 06011 Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy.

Uncontrolled Phase II Clinical Studies:

Study Design

Two phase 2 studies were submitted. Both studies (95-11 and 97-19) were international, single arm, fixed regimen, multicenter studies which enrolled patients with primary or secondary MDS patients of all five FAB subtypes.

Both studies used a similar DAC dosage regimen (15 mg/m^2 infused IV over 4 hours every 8 hours for 3 consecutive days of a 6-week cycle). A minimum of two courses and a maximum of 6 courses could be administered, although a few patients received eight. Patients who achieved CR, PR or stable disease (SD) after two courses received two additional courses. Patients who relapsed or progressed were taken off the study.

In both phase II studies, the primary endpoints were: best hematological response, duration of response, and overall survival.

Results

For details on enrollment criteria and demographics for these studies, please see Dr. Kaminskas' review. The response rate (CR + PR) ranged from 24-26% for both studies. In PCH 95-11 the median duration of CR + PR was 250 days, and the mean duration was 263±21.3 (SD) days. In PCH 97-19 the median duration

of CR + PR was 146 days, and the mean duration was 148±25 (SD) days. In PCH 95-11 the median survival was 401 days. In PCH 97-19 the median survival was 468 days.

Phase 3 trial

The sponsor submitted the results from one large, open-label, randomized, phase 3 trial of decitabine versus supportive care in adults with advanced stage International Prognostic Scoring System (IPSS) classification: Int-1, Int-2, and High risk) myelodysplastic syndrome, D-0007. Randomization was stratified by study center, IPSS classification and type of MDS (i.e., *de novo* vs. secondary). Both treatment groups received standard medical care/supportive care for MDS which included use of PRBCs and/or platelets; prophylactic antibiotics; colony-stimulating factors; erythropoietin and thrombopoietin; and hospitalization). In addition, patients in the Dacogen arm received Dacogen Injection as nine 15 mg/m^2, three-hour infusions over three days per cycle. The trial had two primary endpoints: overall response rate (complete or partial) according to the International Working Group (IWG) criteria and time to progression to acute myeloid leukemia or death. The Response criteria encompass the need for transfusion. Secondary endpoints included survival, transfusion requirements, overall response rate plus the rate of hematological improvement (a lesser than partial response), quality of life measures, and cytogenetic response.

Demographics were well-balanced for gender, age, race, IPSS subgroups, FAB classifications, mean time from diagnosis, and prior MDS therapy. Median age for the trial was 70 years with a range of 62-76 years. Sixty eight percent of patients enrolled were males and thirty-two percent were females. Approximately 87% of the patients had de novo and 13% secondary MDS. Twenty-seven percent had prior MDS therapy. Thirty-one percent of patients had Intermediate-1 IPSS, forty-four percent had Intermediate-2 IPSS, and twenty-six percent had High Risk IPSS. Ten patients (12.3%) in the supportive care arm received some form of erythropoietin and five patients (5.6%) in the Dacogen arm during the trial.

The sponsor reported that patients treated with decitabine had an overall response rate of about 17% (in ITT population) as compared to no responses in the supportive care patients. This difference was statistically significant ($p < 0.001$). Decitabine-treated patients in the single-arm studies had overall response rates of 24% and 26% (ITT populations). The sponsor also reported that time to progression to AML or death was not significantly different in decitabine-treated patients from that in supportive care patients (p=0.160).

Reviewer's Comment: Due to the findings of the DSI audit, this reviewer will not delve further into the data and any claims regarding response rate, transfusions

For additional details, please see the Division of Scientific Investigations report.

Conclusions and Recommendations

As stated above, the transfusion data appears too unreliable to be used for an approval decision. This team leader recommends the following options:

1) The sponsor could recollect all transfusion data from source documentation and based on that data recollection submit an amendment to the current NDA revising the endpoints, study report/results, CRFs, data listings, and data sets as necessary. Following the resubmission, DSI would again inspect sites, possibly increasing the number of sites inspected.
2) The sponsor could submit the study report and results from the EORTC 06011 Phase III randomized trial of intravenous low-dose decitabine versus supportive care in elderly patients with primary MDS, secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy when the study is completed.

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/s/

Ann Farrell
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MEDICAL OFFICER