Randomized Open-Label Phase II Study of Decitabine in Patients With Low- or Intermediate-Risk Myelodysplastic Syndromes

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MGI PHARMA, INC.

DACOGEN® (decitabine; 5-aza-2'deoxycytidine)

STUDY NUMBER:	**DACO-026**
STUDY TITLE:	RANDOMIZED OPEN-LABEL PHASE 2 STUDY OF LOW DOSE DACOGEN® FOR INJECTION (DECITABINE) IN PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES
STUDY PHASE:	PHASE 2
IND NUMBER:	71,160
SPONSOR:	MGI PHARMA, INC. 5775 WEST OLD SHAKOPEE ROAD, SUITE 100 BLOOMINGTON, MN 55437-3174
PROTOCOL DATE:	11 December 2007
Amendment #1 Date:	01 May 2008

SUMMARY OF CHANGES INCORPORATED IN PROTOCOL AMENDMENT #1

The major changes incorporated in this Protocol Amendment 1 (01 May 2008) are to:

- Change the study phase from Phase 4 post-marketing to Phase 2, non-registration trial to better reflect the study design.

- Change the Study Dose and Duration to allow patients to receive the second course of therapy without interruption regardless of degree of myelosuppression, instead of only allowing a full first course.

- Provide Investigator with an option to split the subcutaneous injection volume between more than one administration site for patients who require large drug volumes (e.g. 2 mL or more) for each dose.

- Body weight will be collected according to the dosing schedule.

- Clarify that all patients receiving treatment under Schedule A will have vital signs monitored on day 1,2 and 3 prior to study drug administration. The original protocol required vital signs be monitored on day 1 pre-dose only.

- Clarify that there will be a maximum of 80 patients randomized and treated for this study. Approximately 5,000 simulations per scenario were used to evaluate the performance of the adaptive randomization procedure of the Bayesian design under several different scenarios, shown in Appendix C -- Operating Characteristics of Adaptive Randomization. There is 80% power to select a superior schedule if the overall improvement rates are 10% and 30%, respectively. There is an approximate 41% power to select a superior schedule if the overall improvement rates are 20% and 30%, respectively. When both arms have a 10% overall improvement rate, the probability for each one to be selected is about 9.5%, which is equivalent to the Type I error of a Frequentist design.

Other minor administrative changes to the protocol are displayed in Appendix F - Summary of Changes. Minor editorial changes that do not affect the conduct of the study (i.e. to correct typographical errors and formatting) are not described.

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase (SGPT)
AML	acute myelogenous leukemia
AST	aspartate transaminase (SGOT)
CFR	Code of Federal Regulations
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FAB	French-American-British
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hgb	Hemoglobin
HI	hematologic improvement
ICH	International Conference on Harmonisation
Int-1	Intermediate 1
Int-2	Intermediate 2
IPPS	International Prognostic Score System
IRB	Independent Review Board
IWG	International Working Group
LINE	Relative Long Interspersed Nucleotide Elements
MDS	myelodysplastic syndromes
µg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NCI	National Cancer Institute
NDA	New Drug Application
RBC	red blood cell (count)
SAE	serious adverse event
SQ	Subcutaneous

STUDY SYNOPSIS

Study Title: Randomized Open-Label Phase 2 Study of Low Dose DACOGEN® for Injection (Decitabine) in Patients with Low or Intermediate 1 Risk Myelodysplastic Syndromes

Objectives: The Primary Objective of this study is to determine the clinical activity (overall improvement rate), safety, and tolerability of two different low-dose schedules of DACOGEN® for Injection (called decitabine throughout the rest of this protocol) in patients with Low or Intermediate-1 risk myelodysplastic syndromes (MDS).

The secondary objectives of this study are to assess:

- Hematologic improvement (HI)
- Transfusion requirements
- Cytogenetic response
- Toxicity
- Overall survival

Trial Design: This is a randomized open-label Phase 2 efficacy and safety study of two (2) subcutaneous (SQ) dosing schedules of decitabine in subjects with Low or Intermediate-1 risk MDS. In Schedule A, decitabine will be dosed SQ at 20 mg/m^2/day for 3 consecutive days (1 to 3) every 28 days. In Schedule B, decitabine will be dosed SQ at 20 mg/m^2/day 1 time every 7 days for 21 days (Day 1, 8, and 15) followed by 7 days without an administration of decitabine. This study will be conducted at approximately 6 study centers in the United States.

The primary efficacy outcome is the overall improvement rate (Complete Remission [CR] + Partial Remission [PR] + Marrow CR + Hematologic Improvement [HI]).

The probability that one schedule is superior to the other will be estimated, and the level of toxicity for each schedule will also be evaluated.

Study Duration: For both dosing schedules, a cycle will be considered 28 days. Patients may continue on study drug for additional cycles provided that, in the Investigator's opinion, the patient continues to receive or might receive clinical benefit, with continued dosing, without unacceptable toxicities. Patients can continue to receive therapy for approximately one year on this study.

Study Population: A maximum of 80 patients, age 18 years or older, with de novo or secondary MDS with an IPSS risk classification of Low or Intermediate-1, will be enrolled.

Study Treatments: The initial 40 patients enrolled will be randomized to either Schedule A or Schedule B (20 patients per schedule). The next 40 patients will be enrolled in an adaptive randomization schedule based on the results of previous patients, until a preferred treatment schedule has been identified or the maximum of 80 patients have been enrolled. Patients enrolled after a preferred treatment schedule has been identified, will be enrolled under that schedule.

Efficacy Assessments: Efficacy will be assessed using the modified International Working Group (IWG) Criteria (*Cheson et al., 2006*), as shown in Appendix D and Appendix E.

Safety Assessments: Safety evaluation will include assessments of adverse events (AEs), medical history, physical examinations, vital signs, concomitant medications, and laboratory assessments at baseline and throughout the study period.

Statistical Methods: A complete Statistical Analysis Plan will be completed prior to database lock.

1. INTRODUCTION

MDS consist of a group of myeloid disorders characterized by peripheral blood cytopenias, bone marrow failure, and a risk of transformation to acute myelogenous leukemia (AML). MDS affects more frequently patients of advanced age that are not generally candidates for intensive chemotherapy or bone marrow transplantation strategies. MDS can be classified using different systems such as the French-American-British (FAB) or the World Health Organization (WHO) classifications. Because these two classification systems do not account for age or cytogenetics, they have limited value in predicting survival and AML evolution in patients with MDS.

The International Prognostic Score System (IPSS) (*Greenberg et al, 1997*) is a classification system for MDS that allows the calculation, based on a number of variables, of the expected median survival and progression to AML. With this scoring system patients are divided into categories, Low, Intermediate 1 (Int-1), Intermediate 2 (Int-2), and High-risk, based on percentage of marrow blasts, cytogenetic alterations, and number of cytopenias (Table 1-1).

Table 1-1 IPSS for MDS: Survival and AML Evolution

Prognostic Variable	**Score Value**				
	0 (Low)	**0.5 (Int-1)**	**1.0 (Int-1)**	**1.5 (Int-2)**	**2.0 (Int-2)**
BM blasts (%)	<5	5-10	--	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			
Scores are as follows: Low: 0; Int-1: 0.5 to 1.0; Int-2, 1.5 to 2.0, and high risk ≥2.5 points. *Good karyotype includes: -Y, del(5q), del(20q); Poor karyotype includes: complex (≥3 abnormalities) or chromosome 7 abnormalities; Intermediate karyotype, all others. From *Greenberg, et al, 1997*					

Table 1-2 summarizes the expected overall survival based on age and IPSS score.

Table 1-2 Age Related Survival and AML Evolution of MDS Patients within the IPSS Subgroups

	Number of pts	**Low**	**Int-1**	**Int-2**	**High**
Median Survival (yr)					
Total number of pts (%)	816	267 (33)	314 (38)	176 (22)	59 (7)
Median (yr)		5.7	3.5	1.2	0.4
Age (yr)					
≤60	205 (25)	11.8	5.2	1.8	0.3
>60	611	4.8	2.7	1.1	0.5
≤70	445(54)	9.0	4.4	1.3	0.4
>70	371	3.9	2.4	1.2	0.4
25% AML Evolution (yr)					
Total number of pts (%)	759	235 (31)	295 (39)	171 (22)	58 (8)
Median (yr)		9.4	3.3	1.1	0.2
Age (yr)					
≤60	187 (25)	>9.4 (NR)	6.9	0.7	0.2
>60	572	9.4	2.7	1.3	0.2
≤70	414 (55)	>9.4 (NR)	5.5	1.0	0.2
>70	345	>5.8 (NR)	2.2	1.4	0.4
NR = not reached From *Greenberg, et al, 1997*					

At present the standard of care for patients with lower risk disease is limited to growth factor support, in particular in patients with low-risk IPSS, until there is evidence of disease progression (clinical significant cytopenia, systematic anemia, thrombocytopenia, neutropenia, etc.). This is based on the IPSS data indicating patients with lower risk disease (Low and Int-1 subgroup) have an age-based estimated survival of 2.4 to 11.8 years.

A recent analysis by Garcia-Manero, et al, of the prognosis of patients with lower risk MDS (in the Low and Int-1 subgroup) was performed using data from patients referred to the M. D. Anderson Cancer Center from 1976-2005 (*Garcia-Manero et al. 2008*). Of the 856 patient data sets analyzed, a significant percentage of untreated patients (80%) had a poor prognosis, and 90% of patients died with MDS, that is before experiencing progression to AML.

This study will explore the effect on patient outcomes of low-dose decitabine in the Low and Int-1 MDS population.

2. STUDY OBJECTIVES

2.1 Primary Objective

The Primary Objective of this study is to determine the clinical activity (overall improvement rate), safety, and tolerability of two different low-dose schedules of DACOGEN ® for Injection (called decitabine throughout the rest of this protocol) in patients with Low or Intermediate-1 risk myelodysplastic syndromes (MDS).

2.2 Secondary Objectives

The secondary objectives of this study are to assess:

- Hematologic improvement (HI)
- Transfusion requirements
- Cytogenetic response
- Toxicity
- Overall survival

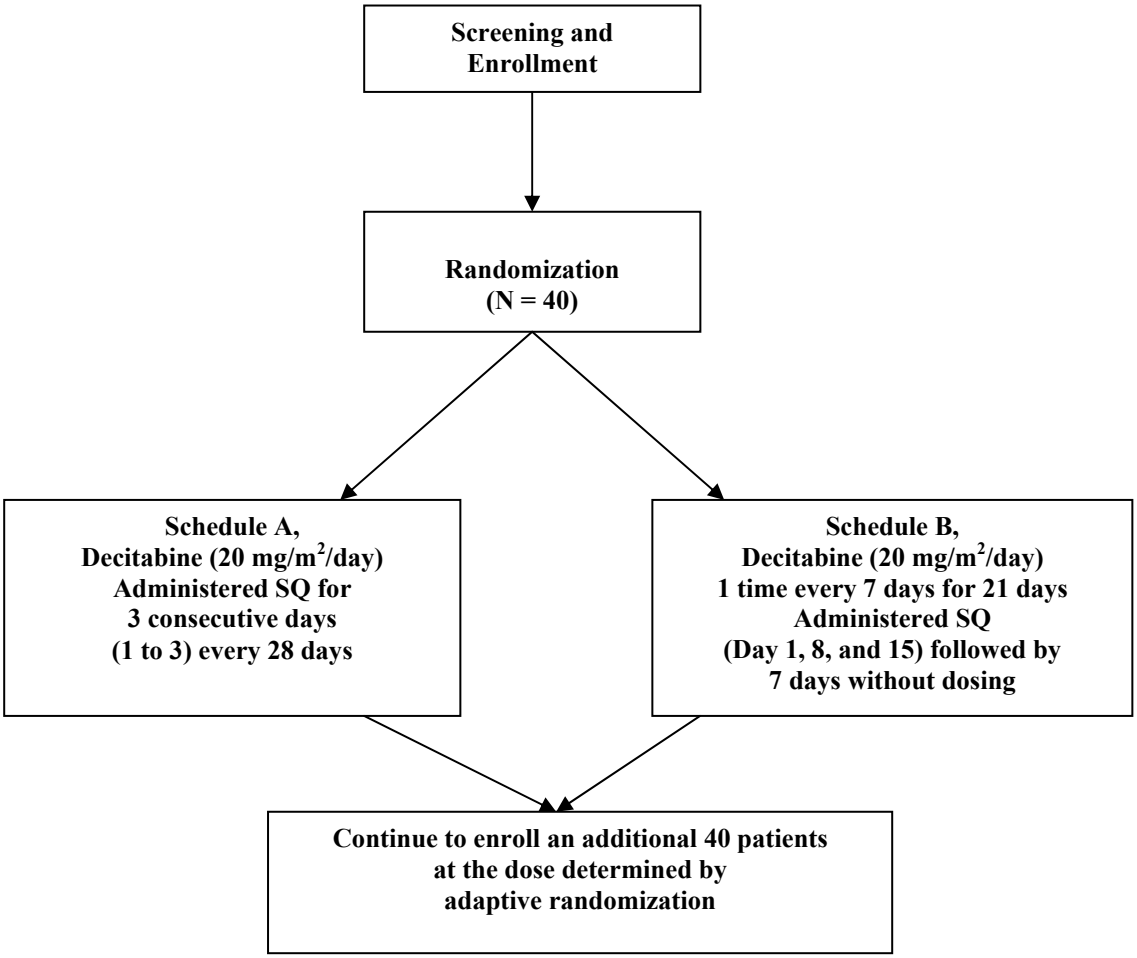
2.3 Tertiary Objective

The optional tertiary objective is to assess the molecular effects of decitabine administration using these dosing schedules in this patient population by using DNA methylation and gene expression assays.

3. STUDY DESIGN

This randomized Phase 2, open-label, efficacy and safety study will evaluate patients with lower risk MDS in two different SQ administration schedules of decitabine. The major study events are shown in Figure 3-1.

Figure 3-1 Major Study Events Planned



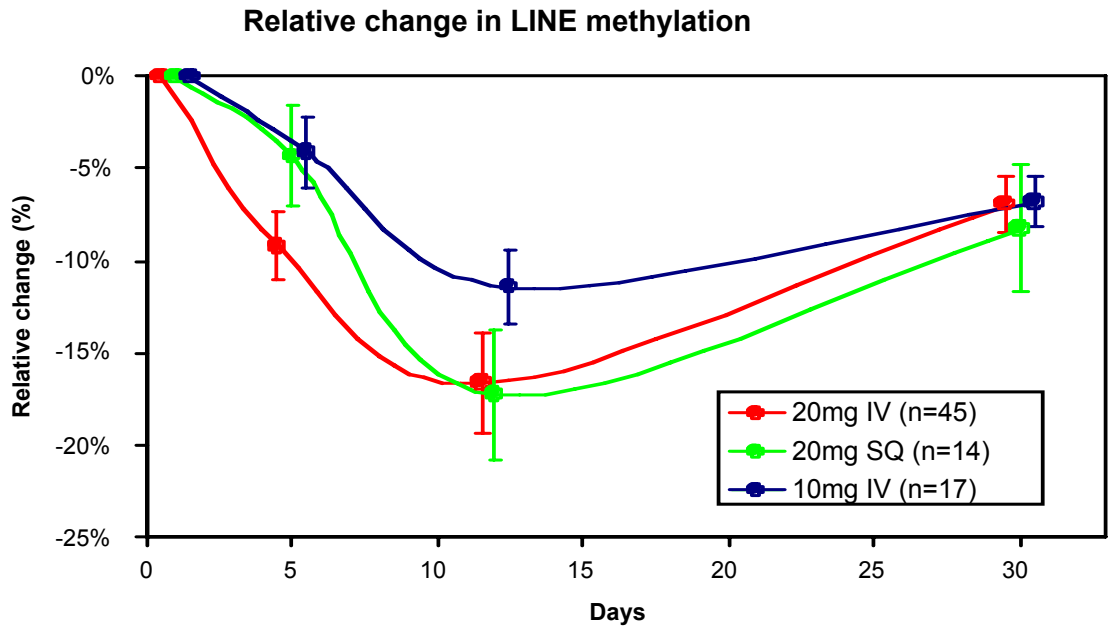
3.1 Rationale for Dose and Administration Methods Used

The rationale of lower doses of decitabine resides in the observation that lower doses of decitabine may be more effective and less toxic by inducing DNA hypomethylation.

In a recent study of decitabine (*Kantarjian et al., 2007*), administration every 28 days was safe and associated with clinical activity. Investigators at M. D. Anderson Cancer Center, in an analysis of the molecular effects of decitabine in patients treated in clinical studies, have suggested potentially more effective schedules of hypomethylation induction (*Kantarjian et al., 2007)*.

Using the LINE 1 assay as a surrogate for global methylation, the administration of decitabine results in induction of hypomethylation that peaks 10 to 15 days after initiation of therapy and gradually normalizes by day 21-28 (Figure 3-2). Administration of more frequent schedules of therapy could potentially be associated with greater induction of hypomethylation.

Figure 3-2 Relative Long Interspersed Nucleotide Elements (LINE) hypomethylation percentage by schedule of decitabine treatment



This concept is currently being evaluated in an ongoing study of the combination of 5-azacitidine/valproic acid and ATRA (*Soriano, et al. 2006*). Preliminary results from this study indicate that therapy can be administered every 3 weeks, with no observed excess toxicity. A 58% CR/CRp rate was documented in older patients with AML and high-risk MDS. Some of these data have been confirmed by in vitro systems in which daily administration of low doses of decitabine to leukemia cells resulted in significant cell kill.

Building on the research at M. D. Anderson and elsewhere, this study will explore if lower doses of decitabine may be more effective and less toxic in inducing DNA hypomethylation in patients with MDS.

3.2 Study Duration and Dates

Patients will receive the second course of therapy without interruption regardless of degree of myelosuppression. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Progressive disease.
- Possibility of undergoing allogeneic bone marrow transplantation.
- Intercurrent illness that prevents further administration of treatment.
- Patient request.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator or treating physician.

After the first course of therapy, the interval between subsequent cycles of therapy may be spaced out ± 3 days at the discretion of the treating physician. However, within each cycle the schedule of study events should be followed as closely as possible.

Patients can continue to receive therapy for approximately one year on this study.

3.2.1 Patient Dose Modification

Patients who show no evidence of life-threatening infection or if they have ≤ Grade 2 extramedullary toxicity (vomiting included) may continue subsequent course of therapy. If patients have Grade 3-4 non-hematological toxicity and the treating physician believes that it is appropriate to proceed with a subsequent course, the patient will receive that subsequent course at a reduced dose level (reduce by one level).

If prolonged myelosuppression (≥42 days) is observed after cycle 1 (see Section 5.1), decitabine will be administered at the next lower dose level as shown in Table 3-1. Therapy can continue as described in Section 3.2, as long as the treating physician judges the patient is benefiting, or might benefit, from treatment.

Table 3-1 Decitabine Dose Reductions

Dose Level	Dose in mg/m^2/day
1	20
-1	15
-2	10
-3	5

4. PATIENT SELECTION

4.1 Study Population

A maximum of 80 patients are planned for enrollment. Male and female patients at least 18 years of age with de novo or secondary MDS and an IPSS risk classification of low or intermediate-1 risk, who meet all of the inclusion and none of the exclusion criteria below will be considered eligible for enrollment.

4.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Male or female patients age 18 years and older;
2. Patients must sign an institutional review board (IRB)-approved informed consent form, and understand the investigational nature of this study and its potential hazards prior to initiation of any study-specific procedures or treatment;
3. Must have ECOG performance status of 0-2;
4. Adequate renal and hepatic function (creatinine < 2 times upper limit of normal, total bilirubin of < 2 times upper limit of normal, and AST and ALT ≤ 2 times upper limit of normal) unless proven to be related to disease infiltration.
5. Female patients need a negative serum or urine pregnancy test within 7 days prior to study drug administration (applies only if patient is of childbearing potential. Non-childbearing is defined as ≥ 1 year postmenopausal or surgically sterilized);
6. Women of childbearing potential and men must use contraception. Men and women must continue birth control for the duration of the study;
7. Patients with low or intermediate-1 risk MDS by the IPSS classification (as defined in Table 1-1);

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Women who are pregnant or nursing;
2. Those who have received prior therapy with decitabine
3. Prior therapy with azacitidine (Vidaza®)
4. Those who received growth factor support or lenalidomide in the 30 days prior the first dose of decitabine.
5. Those who have received an investigational agent 30 days prior to the first dose of decitabine,
6. Patients with active, uncontrolled, systemic infection considered opportunistic, life threatening or clinically significant; or any severe, concurrent disease, which, in the judgment of the Investigator and after discussion with the Sponsor and Primary Investigator, would make the patient inappropriate for study entry.

5. STUDY TREATMENT(S)

5.1 Treatments Administered

All patient enrollments will be registered through an Interactive Voice Response Services (IVRS) system prior to dosing. All decitabine doses will be given at the study site, either on in-patient or out-patient status. Due to the volume of drug that may be needed by some patients, at the discretion of the investigator, dosing may be done in one or multiple injections, given during the same drug administration session(s), particularly if the volume is > 2mL.

Two schedules of decitabine will be studied, as shown in Appendix B.

Patients will receive the second course of therapy without interruption regardless of degree of myelosuppression. Patients can continue to receive therapy, as described in Section 3.2, as long as the investigator feels that patient is benefiting, or might benefit, from decitabine (see below). After the first course of therapy, at the discretion of the treating physician, the interval between the subsequent cycles of therapy can be spaced out ± 3 days. However, within each cycle the schedule of study events should be followed as closely as possible.

If prolonged myelosuppression (≥ 42 days) is observed after cycle 1 (defined by an absolute neutrophil count [ANC] of < 1 $x10^9$/L and a platelet count of < 30 $x10^9$/L), then subsequent cycles of decitabine will be given at the next lower dose (see Table 3-1), once the counts recover.

Count recovery will be defined as an ANC ≥1 x10^9/L and platelets > 50 x10^9/L. Subsequent cycles of therapy will be administered when the counts recover to a level that is satisfactory to the treating physician.

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- The study is closed.
- Progressive disease.
- Possibility of undergoing allogeneic bone marrow transplantation.
- Intercurrent illness that prevents further administration of treatment.
- Patient request.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator or treating physician.

5.2 Method of Assigning Patients to Treatment Groups

The first 40 patients enrolled will be randomized to receive the study treatment on either Schedule A or Schedule B (20 patients per Schedule). As shown in Appendix C, the next 40 patients will be randomized to receive decitabine in either Schedule A or Schedule B (Appendix B) using an adaptive randomization procedure which bases assignment probabilities on observed results in preceding patients.

5.2.1 Blinding and Unblinding

This is an open-label study so no unblinding procedures are necessary.

5.3 Concomitant Therapy

Permitted growth factor use includes erythropoietin for hemoglobin < 10 g/dL, and G-CSF for fever unknown origin, infection and/or ANC < 0.75 x10^9/L.

Therapy with growth factor support (other than indicated above), lenalidomide, azacitidine (Vidaza), or other investigational agents is not permitted during the study.

5.4 Restrictions

5.4.1 Fluid and Food Intake

There are no restrictions.

5.5 Treatment Compliance

Because decitabine will be administered subcutaneously at the investigational sites, monitoring of patient compliance to treatment is assured.

5.6 Treatment Description(s)

5.6.1 Decitabine (DACOGEN®) for Injection

Decitabine (DACOGEN®) for Injection is a commercially available agent indicated for treatment of patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo, and secondary MDS of all FAB subtypes (RA, RARS, RAEB, RAEB-t, CMML) and Intermediate-1 and Intermediate-2, and High Risk IPSS groups.

5.6.1.1 Pharmaceutical data

Decitabine 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.

Decitabine should be stored at USP Controlled Room Temperature (20°C to 25°C, with excursion permitted 15°C to 30°C). Reconstitution of the powder results in a rapidly decomposing solution, as described in Section 5.8.

5.6.2 Precautions

Decitabine is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised in handling and preparation. Skin contact with the solution should be avoided and protective gloves should be worn. Drug spilling can be inactivated by 2 M sodium hydroxide

solution. The skin should be treated with a borax buffer solution pH 10 and after that thoroughly washed with water and soap.

5.7 Packaging and Labeling

The drug product that will be supplied for this protocol is specifically manufactured and labeled for investigational use. The investigational supplies are labeled as Decitabine for Injection. Each vial of Decitabine for Injection is packaged in a single vial carton, and includes a package insert with storage stability and drug handling information. Each vial of decitabine is labeled with the following information:

- Study drug name: Decitabine for Injection
- Lot number
- Expiration Date
- Amount of drug per vial
- Name and address of Sponsor
- Storage conditions
- Name of manufacturer
- Caution Investigational Drug statement

5.8 Study Drug Preparation

Occupational Safety and Health Administration (OSHA) Guidelines for handling cytotoxic drugs outlined in the American Journal of Hospital Pharmacy must be followed.

Reconstitute a new vial using 5 mL of sterile water for injection. Visually inspect the resulting solution to verify that it is free of particulates. The reconstituted product must be used within 30 minutes of its preparation. Residual solution cannot be used. When reconstituted with 5 mL of sterile water for injection, each mL will contain 10 mg of decitabine and 13.6 mg of KH_2PO_4.

5.9 Study Drug Administration

For all patients, study drug should be administered in the clinic. Each SQ injection will be administered at one of several suitable anatomic sites (e.g. abdomen, thigh, upper arm) on a

rotating basis. For patients who require a large volume (i.e., > 2 mL) of drug be administered, multiple injections during the same administration session are permitted at the discretion of the investigator.

5.10 Storage and Accountability

Decitabine will be shipped to the site pharmacy when all initiation documents, including IRB approval and IRB-approved Informed Consent, have been received and reviewed by the Sponsor. Shipment of drug to the site signifies initiation of the study. The sites are instructed to store decitabine vials at 25°C (77°F) with excursions permitted to 15 - 30°C (59 - 86°F) in a secure area with limited access. Decitabine (Dacogen®) for Injection will be supplied by MGI PHARMA, INC, Bloomington, MN, USA.

An accurate record of shipment receipt and dispensing of test medication will be maintained by the Principal Investigator or designee. These records will be available for inspection by MGI, its representatives, and the Food and Drug Administration (FDA) at any time. A copy of the study drug inventory will be provided to the Sponsor at the conclusion of the study or as the record is completed.

Drug supplies for this study are to be used only in accordance with this protocol and under the supervision of the Principal Investigator. The Principal Investigator must insure that any unused study drug be returned to MGI or destroyed per instructions by MGI. Periodically throughout and at the conclusion of the study, supplies of decitabine may be inventoried by MGI or its designee.

An initial supply of decitabine will be provided to each site's pharmacy. Thereafter, it is the responsibility of the trial pharmacist to order a resupply. Resupply requests should be submitted to MGI at least 5 days before the requested shipment date.

5.11 Investigational Product Retention at Study Site

Procedures for proper handling and disposal of antineoplastic drugs should be applied. All used decitabine vials may be destroyed according to the site's cytotoxic/chemotherapy waste disposal policy.

6. STUDY PROCEDURES

The schedule of study procedures is shown in detail in Appendix A and is described below.

6.1 Informed Consent

A properly executed informed consent, which has been approved by the IRB and in compliance with United States (US) Code of Federal Regulations (CFR) Title 21, Part 50 (21 CFR 50), shall be obtained from each patient prior to admission to this study or prior to performing any unusual or non-routine study-related screening procedure that involves a risk to the patient. The Principal Investigator shall provide a copy of the signed informed consent to the patient and will keep the original signed form in the patient's study file. The US FDA Protection of Human Subjects (21 CFR 50.25) regulation contains a complete discussion of this requirement.

6.2 Screening/Pre-Treatment Visit Assessments

All pretreatment assessments should be obtained within 14 days prior to randomization into the study. Clinical laboratory samples, with the exception of the peripheral blood samples obtained as part of the optional sampling described in Section 6.5.1, will be processed and analyzed using the laboratories at the individual study centers.

Samples for the optional tertiary objectives will be sent to M.D. Anderson Cancer Center, as described in the Study Procedures Manual.

The following will be completed:

- Informed Consent
- Medical History
- Monitoring of concomitant medications and transfusions
- Physical Exam
- Pregnancy Test (if applicable)
- IPSS assessment of disease
- ECOG Performance Status
- Body Weight
- Vital Signs
- Hematology
- Blood Chemistry
- Cytogenetics – complete within 1 month prior to randomization
- Peripheral blood sampling
- Bone marrow aspirate
- Verify patient meets all of the inclusion criteria and none of the exclusion criteria

After a patient has signed informed consent, completed all of the pre-treatment screening assessments, eligible patients will be randomly allocated to dosing Schedule A or Schedule B (Appendix B) by a central procedure up to 4 days before initiation of study treatment, if applicable. However, it is recommended that study treatment be started as soon as possible after patients are assigned to a treatment.

6.3 Assessments Occurring During the Drug Cycles

One cycle is considered 28 days. Study drug administration will follow one of two schedules. **Schedule A**, decitabine is given SQ (20 mg/m^2/day) for 3 consecutive days (Day 1 to 3) every 28 days; **Schedule B**, decitabine is given SQ (20 mg/m^2/day) once every 7 days for 21 days (Day 1, 8, and 15) followed by 7 days without an administration of decitabine.

6.3.1 Cycle One Only

Occurring on Day 1 only:

- Physical Exam
- ECOG Performance Status

Occurring throughout the cycle:

- Continued monitoring of concomitant medications and transfusions
- Body Weight Day 2, 3, 8 and 15 (Day 2 and 3 are only for those patients receiving treatment under Schedule A; Day 8 and 15 are only for those patients receiving treatment under Schedule B).
- Vital signs Day 1,2, 3, 8, 15, and 22 (Day 2 and 3 are only for those patients receiving treatment under Schedule A). Vital signs should be obtained prior to study drug administration.
- Hematology at days 1, 8, 15, and 22
- Blood chemistry at days 1, 8, 15, and 22
- Decitabine administration based on appropriate dosing schedule (shown for both groups in Appendix B)
- Peripheral Blood will be collected on the following schedule:
  - Patient Randomized to Schedule A: Day 1, 3, 5, 8, 15, 22. All samples will be obtained prior to drug administration, when possible.
  - Patient Randomized to Schedule B: Day 1, 3, 8, 15, 22. All samples will be obtained prior to drug administration, when possible.
- Begin monitoring for adverse events at Randomization.

6.3.2 For all Subsequent Cycles

Occurring on Day 1 only:

- Physical Exam
- ECOG Performance Status

Occurring throughout the cycle:

- Continue monitoring of concomitant medications and transfusions
- Body Weight per dosing schedule.
- Vital signs at all visits (to be obtained before study drug administration)
- Hematology at days 1, 8, 15, and 22
- Blood chemistry at days 1, 8, 15, and 22
- Cytogenetics will be performed in tandem with the bone marrow assessments described below
- Bone marrow aspirates in cycle 2, 3 and then every subsequent 3rd cycle must be obtained within 7 days prior to the start of the next cycle. (If patients have a documented complete remission, an additional bone marrow aspirates must be performed at the end of the next cycle after initial documentation of CR. After this, patients with CR are not required to have additional bone marrow assessments until clinically indicated).
- Decitabine administration based on appropriate dosing schedule (Appendix B)
- Peripheral Blood will be collected on the following schedule:
  - Patient Randomized to Schedule A: Day 1, 8, 15, 22. All samples will be obtained prior to drug administration, when possible.

  - Patient Randomized to Schedule B: Day 1, 8, 15, 22. All samples will be obtained prior to drug administration, when possible.
- Continued monitoring for adverse events

6.4 End of Study Assessments

The End of Study Assessments listed should be performed prior to patient discharge from the study, as described in Section 3.2 and Section 6.8.

- Continue monitoring of concomitant medications and transfusions
- Physical Exam
- ECOG Performance Status
- Body weight
- Vital signs
- Hematology
- Blood chemistry
- Cytogenetics will be performed in tandem with the bone marrow assessments described below.
- Bone marrow aspirate assessment. Patients are not required to have a bone marrow assessment if they have had a documented assessment within 4 weeks prior to discontinuation. (Note: After consultation with the Sponsor, repeat bone marrows are not necessary if the patient has a non-response or progressive disease that can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC $\leq$ 0.3 if the bone marrow test is considered non-contributory by the investigator at any time point.)
- Peripheral Blood collection (Note: If a site participates in the optional peripheral blood draws for assessment of DNA methylation and gene expression, then these samples will be sent to M.D. Anderson for processing and review. Details of the sample shipment requirements etc, are provided in the study procedure manual).
- Continue monitoring for adverse events

6.5 Efficacy Assessments

Criteria for response will follow the modified 2006 IWG criteria (*Cheson et al., 2006*). These are summarized in Appendix D and Appendix E.

6.5.1 Modification of Molecular Targets - Optional

The tertiary objective of this study is to assess the molecular effects of decitabine administration using the dosing schedules shown in Table 6-1 and Table 6-2. Patients will be given the option to participate in the assessments of DNA methylation and gene expression. The cycle 1 assessments are performed on peripheral blood samples obtained prior to dosing as shown below

in Table 6-1 for patients randomized to Schedule A, and in Table 6-2 for patients randomized to Schedule B. For subsequent cycles, peripheral blood will be obtained prior to each cycle of therapy and then weekly thereafter.

Table 6-1 Schedule A: Peripheral Blood Collection

Assay	**Collection Days**
DNA methylation	1, 3, 5, 8, 15, 22
Gene expression	1, 3, 5, 8, 15, 22

All Schedule A samples will be obtained prior to drug administration, when possible.

Table 6-2 Schedule B: Peripheral Blood Collection

Assay	**Collection Days**
DNA methylation	1, 3, 8, 15, 22
Gene expression	1, 3, 8, 15, 22

All Schedule B samples will be obtained prior to drug administration, when possible.

Because a number of different assays will be utilized to assess the effects of decitabine on methylation, the intention of the correlative studies is not to draw statistical conclusions in terms of the optimal biological dose of the agents studied here; rather, these represent pilot studies that will further the understanding of the in vivo mechanism of action of decitabine to aid in the design of future studies.

6.5.1.1 Analysis of DNA methylation

Both global and gene specific assays of DNA methylation will be performed. For global DNA methylation, the LINE assay using bisulfite pyrosequencing will be used (*Garcia-Manero et al. 2006*). Based on prior experience with MDS a number of genes may be studied with gene specific assays. These genes include, but are not limited to: ER, E-cadherin, p15, and RIL. All genes will be studied using pyrosequencing techniques, and in selected cases, samples could be used for MCA/RDA analysis using the Agilent's CPG array platform (*Garcia-Manero et al. 2006*).

6.5.1.2 Analysis of gene-specific expression

Decitabine has the capacity to induce gene expression reactivation of aberrantly silenced genes. Assays will measure the mRNA of the genes studied for DNA methylation. These assays will all be completed at the MDACC laboratory.

This will be performed using real-time PCR assays previously established at the MDACC laboratory. With this assay, 5 μg of total RNA are treated for 30 min with DNAseI, which is then inactivated with DNA Free Kit (Ambion). Reverse transcription will be performed using Superscript II (Life Technologies), and DNA products will be assessed and quantified by real-time PCR. GAPDH will be used as control.

6.6 Safety Assessments

Safety evaluation will include assessments of adverse events (AEs), medical history, physical examinations, vital signs, concomitant medications, and laboratory assessments at baseline and throughout the study period.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting MGI or representative to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The Investigator is responsible for appropriate medical care of patients during the study and remains responsible for following AEs that are serious or that caused the patient to discontinue from the study.

All AEs including SAEs will be recorded for all patients beginning immediately after the patient is randomly assigned to a treatment group until 30 days after the date of study drug discontinuation. The patient should be followed until the event resolves or reaches a medically acceptable outcome or the patient is lost to follow-up.

After the 30-day period, only treatment-related events (new or continuing) will be reported and/or followed until resolution, acceptable medical outcome or the patient is lost to follow-up.

6.7 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND REPORTING

6.7.1 Adverse Events

An AE is any change in physical signs, symptoms, and/or clinically significant laboratory change occurring after randomization, regardless of its relationship to study drug. An abnormal laboratory value is considered to be an AE if the laboratory abnormality results in discontinuation from the study and/or is judged by the investigator to be of significant clinical importance. All AEs are to be recorded on the AE case report forms. The dates of duration, intensity, relationship to the study drug, outcome, dose delays, seriousness, and treatment will also be recorded on the case report form.

If treatment is discontinued as a result of an AE, study site personnel must clearly document the circumstances and data leading to discontinuation of treatment, using the appropriate CRF.

6.7.1.1 Severity

When possible, all toxicities observed will be graded according to the NCI CTCAE v3.0. For any toxicity not graded in the NCI CTCAE v3.0, intensity of the AE shall be recorded on the appropriate case report form pages based on the following definitions:

Mild:	Sign or symptom noticeable, but does not interfere with normal daily activities.
Moderate:	Sign or symptom sufficient to interfere with normal daily activities.
Severe:	Sign or symptom is incapacitating with inability to perform daily activities.
Life Threatening:	Sign or symptom significantly increases risk of death.

6.7.1.2 Relationship to Study Drug

The relationship between the administration of the study drug and the AE will be recorded as follows:

Not Related: This category applies to those AEs which, after careful consideration are clearly due to extraneous causes, e.g. disease, environment, etc.

Possibly Related: This category applies when there is modest suspicion that the AE may be related to study medication, but there is also suspicion that other etiologies such as concomitant illnesses, or other medications may be contributing to the event.

Probably Related: This category applies when the event seems to be related to study medication but there is a modest suspicion that it could be related to other causes. An example of this would be asthenia, which seems to get worse after dosing but which the investigator feels could be related to changes in the patient's underlying condition.

Definitely Related: This category applies when there is almost no consideration of other causality.

6.7.2 Serious Adverse Events

An AE will be classified as a serious adverse experience (SAE) when it refers to any event resulting in any of the following:

- Death,
- A life threatening event or condition,
- Requires inpatient hospitalization or prolongation of a hospitalization,
- Persistent or significant disability/incapacity,
- A congenital anomaly/birth defect, and/or
- An important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent an outcome listed above.

Hospitalizations scheduled for study treatment or for a planned medical procedure unrelated to the study will not be reported or collected as SAEs. If a scheduled hospitalization is prolonged due to an AE or SAE for any patient on study, then it must be reported.

6.7.2.1 Reporting Requirements

All SAEs must be reported via fax to the appropriate safety officer (see contact information below) within 24 hours of discovery by the investigator. If a fax is not available, then the report must be made by phone.

MGI Global Drug Safety and Pharmacovigilance contact information is:

Sandra Fielder, MD Telephone: 952-406-3197
Pam Johnson, Pharm.D. Telephone: 952- 406-3185
Fax #: +1 952 346 4940
Phone: 1-800-562-5580
E-mail: drugsafety@mgipharma.com

A written report of any SAE will be provided to the Sponsor on the appropriate SAE form and case report form. The investigator will then make an accurate and adequate report to the Sponsor and to the reviewing IRB/EC on any serious and unexpected AE that may reasonably be regarded as being caused by or associated with the study drug and which was not previously anticipated (in nature, severity, or degree of incidence) in the written information or Investigator's Brochure provided to the investigator by the Sponsor.

Copies of each report will be kept in the investigator's study file and adequate documentation will be provided to the Sponsor, including documentation that the IRB/EC has been notified of such SAEs. Reports of all serious and unexpected AEs associated with the use of the study drug must be submitted to the applicable health authorities and IRB/EC within 15 calendar days after their disclosure. However, fatal or life threatening experiences associated with the use of the study drug must be reported, via phone, by the Sponsor to the applicable Health Authorities within 7 calendar days of disclosure. A written report must also follow within a 15-day timeframe.

Additional information relative to the patient's subsequent course must be submitted to the Sponsor until the event has been resolved or until an acceptable medical endpoint has been reached.

The following SAEs or outcomes are to be reported to the Sponsor if they become known to the investigator:

1. All SAEs and deaths occurring within 30 days after study drug discontinuation,
2. SAEs occurring after this 30-day time period that are considered by the investigator to be related to study treatment, or
3. The occurrence of a congenital anomaly up to 11 months after study completion.

SAEs should be followed by the investigator until resolution, medically acceptable outcome, or the patient is lost to follow-up.

6.8 Removal of Patients from Therapy or Assessment

The Investigator may withdraw a patient from the study for any of the following reasons:

- Progressive disease.
- Possibility of undergoing allogeneic bone marrow transplantation.
- Occurrence of a serious or intolerable adverse event.
- Emergence of a clinically significant change in a laboratory parameter(s).
- The Sponsor or investigator terminates the study.
- The patient requests to be discontinued from the study.
- A protocol violation sufficiently serious as to require patient withdrawal.
- General or specific changes in the patient's condition that render further treatment unreasonable or unsafe within the standards of clinical practice in the judgment of the investigator or treating physician.

6.9 Patient Follow-up

Approximately 30 days after receiving the last dose of study drug, patients will be assessed for toxicity, patient status, and relapse/progression, if applicable. Thereafter patients will be

assessed for initiation of subsequent therapy, patient status and relapse/progression, if applicable, every 2 months until death, lost to follow-up, or until the Sponsor terminates the study.

7. STATISTICAL CONSIDERATIONS

7.1 Determination of Sample Size

There will be a maximum of 80 patients randomized and treated for this study. Approximately 5,000 simulations per scenario were used to evaluate the performance of the adaptive randomization procedure of the Bayesian design under several different scenarios, shown in Appendix C -- Operating Characteristics of Adaptive Randomization. There is 80% power to select a superior schedule if the overall improvement rates are 10% and 30%, respectively. There is an approximate 41% power to select a superior schedule if the overall improvement rates are 20% and 30%, respectively. When both arms have a 10% overall improvement rate, the probability for each one to be selected is about 9.5%, which is equivalent to the Type I error of a Frequentist design.

7.2 Appropriateness of Measures

7.2.1 General Considerations

For continuous variables, data will be summarized with mean, SD, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with number and proportion for each category by treatment group.

All efficacy endpoints will be analyzed in mITT and PP populations. The primary analysis population is mITT. Demographics and baseline characteristics will be analyzed using the mITT population. Safety endpoints will be analyzed using the safety population.

Because adaptive randomization will be applied to patients starting with the 41st patient, the response data from the previous evaluable patients will be analyzed in a dynamic fashion to decide which treatment schedule the next patient will be assigned.

7.2.2 Analysis Populations

Modified Intent-to-Treat - The modified intent-to-treat (mITT) population will be defined as all patients randomly assigned to a treatment group who receive at least one dose of the assigned treatment. For efficacy analysis, mITT is the primary analysis population.

Per-Protocol - The per-protocol (PP) population will be defined as all patients randomly assigned to a treatment group who receive at least two cycles of treatment with no major protocol deviations (e.g. ineligibility, missing assessments). Patients who die or discontinue for progressive disease prior to receiving two cycles will be included. Patients excluded from the PP cohort will be identified prior to a database lock. For efficacy analysis, PP is the secondary analysis population.

Safety - The safety population will be defined as all patients randomly assigned to a treatment group who receive at least 1 dose of study drug.

Subgroup Populations

The following subgroups (if there are sufficient numbers of patients with these subgroups) will be explored for their effects on the primary efficacy endpoint and some of the secondary efficacy endpoints:

- IPSS classification (low vs Intermediate-1)
- Age (<65 years, 65-74 years, ≥ 75 years)
- Time from MDS diagnosis (diagnosis (< 6 months and ≥ 6 months)
- Type of MDS (*de novo*, secondary MDS)
- Prior MDS therapy
- Baseline cytogenetic classification of risk
- Baseline cytogenetic abnormality
- Baseline performance status

7.2.3 Interim Analyses

Patient data are monitored continuously without suspending accrual (see Section 7.2.4.1.2).

7.2.4 Efficacy Measures and Analyses

7.2.4.1 Primary Efficacy Measures and Analyses

7.2.4.1.1 Primary Endpoint

Overall improvement is defined as a patient having a complete remission (CR), partial remission (PR), Marrow CR, or hematologic improvement (HI) as defined by the modified International Working Group (IWG) response criteria for MDS in Appendix D. After patients complete each cycle, patient responses to the treatment will be evaluated according to the criteria in Appendix D. For each patient, the best response among all responses from previous evaluations will be used for calculation of overall improvement rate. Patients not having a response assessment due to missing data will be regarded as a failure in the ITT analysis.

7.2.4.1.2 Primary Analysis

Patients will be assigned to receive decitabine as described (Schedule A or Schedule B), using an adaptive procedure that bases assignment probabilities on observed results in preceding patients. At first, 20 patients will be assigned to each schedule with equal probability using blocked randomization. As efficacy data accrues, patient assignment to the two schedules will become unbalanced in favor of the schedule that has the higher overall improvement rate (OR).

Based on previous studies, an overall improvement rate of about 20% is expected in both arms. Therefore, it is assumed OR has a prior Beta distribution (0.4, 1.6) with mean 0.20. Let ORa and ORb denote the overall improvement rates for schedule A and schedule B, respectively. Beginning with the 21st patient in each arm and for each subsequent patient, we will compare ORa with ORb, incorporating available data from all patients with evaluable response. Patients must be on treatment for at least 3 cycles in order to be eligible for evaluation of response status. In order to avoid favoring one arm earlier in a large study, instead of assigning patients with posterior probability (Pa=Pr(ORa>ORb|data) and Pb=1-Pa), the following formula to assign patients is used:

$$Aa=\frac{\sqrt{Pa}}{\sqrt{Pa}+\sqrt{Pb}},\ Ab=1-Aa,$$

where Aa is the probability of assigning patients to schedule A, Ab is the probability of assigning patients to schedule B, Pa is the posterior probability that schedule A is superior to schedule B and Pb is the posterior probability that schedule B is superior to schedule A.

If at any point during the study Pr(ORa>ORb|data)>0.95(or <0.05) the schedule A(or B) will be selected as superior. If accruing information gives strong evidence that a OR of 10% or greater is unlikely to be true for any one of the treatment arms (Pr(ORa >0.1|data)<0.05, or, Pr(ORb >0.1|data)<0.05), assignment to that arm will be stopped. If the maximum of 80 patients is enrolled and evaluated (the last patient has been on treatment for 3 cycles) and Pr(ORa>ORb|data)>0.95 (or <0.05), we will declare that schedule A(or B) has a higher OR rate than schedule B (or A). Otherwise, the study will be inconclusive. The operating characteristics of this design are included Appendix C.

7.2.5 Secondary Efficacy Measures/Analyses

7.2.5.1 Hematologic Improvement (HI)

Hematologic improvement will be defined using the 2006 IWG response criteria for MDS.
HI will be calculated along with an exact 95% confidence interval for each treatment arm.
Patients not having a response assessment due to missing data will be regarded as a failure in the ITT analysis.

7.2.5.2 Transfusion Independence

A patient is considered *independent at baseline* if they had no transfusions in the 8 weeks prior to the date of first dose. Transfusions occurring on the date of first dose will be considered to be 'on-study' transfusions.

A patient must be transfusion-free for ≥ 8 consecutive weeks (56 days) between the date of first dose and study treatment discontinuation date to be considered *independent while on study*. A

patient is *transfusion dependent on study* if there is no 8-week period between first dose and treatment discontinuation without a transfusion.

The *duration of transfusion independence* is measured from the first of the consecutive days during which the patient is free of transfusions (no earlier than the date of first dose) to the date of the first transfusion after this period; the duration is censored at the date of study treatment discontinuation. For patients who are still ongoing at the time of analysis, duration will be censored on the date of last contact.

Transfusion independence will be summarized separately for RBCs and platelets. The rate of on-study transfusion independence will be calculated. The duration of transfusion independence will also be tabulated.

7.2.5.3 Cytogenetic Response

The number and percent of patients with a cytogenetic response will be summarized by treatment group. In order to be included in the analysis, a patient must have abnormal cytogenetics at baseline and cytogenetic data for at least one post-baseline visit.

7.2.5.4 Toxicity

Toxicity will be presented in descriptive statistics. The assessments of toxicity (recording of concomitant medications and adverse events) are described in Section 5.3 and Section 6.7.

7.2.5.5 Overall Survival

The time to death will be calculated as the number of days from the date of first dose to the date of death.

Kaplan-Meier product limit estimates will be used to describe time to death. Patients not known to have died by the time of data analysis will be right-censored at the date of last contact.

7.2.5.6 Time to AML Transformation or Death

The time to AML transformation or death will be calculated as the number of days from the date of first dose to the date of AML transformation or death, whichever is earlier.

Kaplan-Meier product limit estimates will be used to describe time to AML transformation or death. Patients not known to have transformed to AML or died by the time of data analysis will be right-censored at the latter of the date of last bone marrow aspirate, bone marrow biopsy, or peripheral blood draw.

7.2.6 Exploratory Analysis

Subgroup analysis for the Optional Tertiary endpoints will be performed by treatment group.

7.2.7 Safety Analyses

Safety data will be analyzed using descriptive statistics.

7.2.7.1 Extent of Exposure

Duration (number of cycles and infusions) of the assigned treatment and doses (cumulative and intensity) will be summarized by treatment group.

7.2.7.2 Adverse Events

All adverse events will be coded using MedDRA. The incidence of treatment-emergent adverse events (number and percent of patients reporting the adverse event at least once during the study) will be summarized by treatment arm. In addition, adverse events will be summarized by investigator attribution of relationship to study medication and by grade (according to the NCI CTCAE v3.0). Similar summaries will be provided for prevalence by treatment cycle.

7.2.7.3 Clinical Laboratory Evaluation

Applicable clinical laboratory results will be graded according to NCI CTCAE v3.0. Shifts from baseline to maximum grade on treatment will be summarized for each treatment arm. Baseline is

defined as the last result prior to the first dose. If the assessment is on the date of dosing, it will be assumed to be obtained prior to the first dose.

7.2.7.4 Vital Signs, Physical Findings, and Other Safety Observations

Data for vital signs and physical examination at screening visit will be summarized.

7.2.8 Analyses of Molecular Effects of Decitabine

Appropriate data analysis will be explored by research group.

8. DATA MANAGEMENT

Electronic data capture system will be used.

9. MONITORING

All aspects of the study will be monitored by the Sponsor and/or Contract Research Organization (CRO) so authorized by the Sponsor for conformance to the protocol, with respect to good clinical practices, standard operating procedures, and for compliance with applicable government regulations.

The Sponsor/CRO representative will have access to all records and appropriate source documents as necessary to ensure integrity of the data and to review the progress of the study.

10. LIST OF REFERENCES

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APPENDIX A – SCHEDULE OF TRIAL PROCEDURES FOR DACO-026

		Cycle 1								Cycle 2 (±3 Days) through End of Treatment							
	Screening[b]	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**Termination[k]**
Informed Consent[a]	X																
Inclusion/Exclusion Criteria	X																
Medical History	X																
Concomitant Medications/ Transfusions[c]	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X	X	X	X	X	X	X	X
Physical Exam	X	**X**								X							X
Pregnancy Test	X																
Perform IPSS assessment of disease	X																
ECOG performance status	X	**X**								X							X
Body Weight[d]	X	**X**	**A**	**A**		**B**	**B**			X	A	A	B	B			X
Vital Signs	X	**X**	**X[l]**	**X[l]**		**X**	**X**	**X**		X	X[l]	X[l]	X	X	X		X
Hematology[e]	X	**X**				**X**	**X**	**X**		X			X	X	X		X
Blood Chemistry[f]	X	**X**				**X**	**X**	**X**		X			X	X	X		X
Randomization	X																
Drug Administration[g]		**A/B**	**A**	**A**		**B**	**B**			A/B	A	A	B	B			
Cytogenetics[h]	X														7 days prior to start of next cycle		X
Bone Marrow Aspirate [i] (Please see Notes, next page, for timing)	X														7 days prior to start of next cycle		X
Peripheral Blood Sampling for Molecular Correlative Study (optional) [l]	X	**A/B**		**A/B**	**A**	**A/B**	**A/B**	**A/B**		X			X	X	X		X
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X	X	X	X	X	X	X	X

All Table Notes Next Page **Shaded area above is Cycle 1**

Note: The chart above outlines the study procedures required at each visit. One cycle is considered 28 days

Table Notes:

a No study assessments beyond those specified as screening assessments will be performed without obtaining written informed consent.

b The pre-study procedures may be performed within 14 days prior to Randomization.

c Concomitant Medications include transfusions

d Body weight assessed for all patients at Screening, all Cycles Day 1, and Termination. Body weight also assessed per dosing Schedule [Schedule A=Cycle Day 2 and 3, Schedule B=Cycle Day 8 and 15].

e Hematology-All samples will be obtained after drug administration except for screening, when possible.

f Blood Chemistry - All samples will be obtained after drug administration except for screening, when possible.

g Study drug administration will follow one of two schedules:

Schedule A, decitabine is given 20 mg/m2 daily SQ for three consecutive days (days 1, 2, 3) every 28 days;

Schedule B, decitabine is given 20 mg/m2 daily SQ once every seven days (days 1, 8, 15) for 3 consecutive weeks with one week of rest between cycles.

Patients may continue on therapy until they are no longer deriving clinical benefit from therapy. Each SQ injection will be administered at one of several suitable anatomic sites (e.g., abdomen, thigh, upper arm) on a rotating basis. Record the time of drug preparation along with the time and site of drug administration.

h Cytogenetics will be performed at screening and in tandem with the bone marrow assessments during the study and at study discontinuation, as described below. Patients are not required to undergo cytogenetics if they have had a documented clinically indicated assessment within 4 weeks before study discontinuation.

i The pre-study bone marrow aspirate sampling may be performed up to 28 days prior to first dose of study dose. Bone marrow aspirates in cycle 2, 3 and then every subsequent 3rd cycle must be obtained within 7 days prior to the start of the next cycle. If patients have a documented complete remission, an additional bone marrow aspirates must be performed at the end of the next cycle after initial documentation of CR. After this, patients with CR are not required to have additional bone marrow assessments until clinically indicated. Patients are not required to have a bone marrow assessment if they have had a documented assessment within 4 weeks before study discontinuation.

j Peripheral Blood for optional Molecular Correlative study will be collected based on the Randomization schedule during the 1st cycle: After the 1st cycle, peripheral blood for the Molecular Correlative study will be obtained prior to each course of therapy and weekly thereafter as shown in Table 6-1 and Table 6-2

k End of treatment/end of study assessments include adverse events, concomitant medications, including transfusions, physical exam, including weight, vital signs and assessment of ECOG performance status. Laboratory studies including CBC with differential (absolute values) and platelets. (Peripheral blasts should be assessed) Serum chemistries, including bicarbonate, calcium, glucose, BUN, potassium, chloride, sodium, creatinine, total bilirubin, AST, ALT, and alkaline phosphatase. Bone marrow aspirate assessment for morphology and cytogenetics. Peripheral blood smear and aspirate are to be sent to M.D. Anderson for processing and review.

l Vital Sign recording for Day 2 and 3 are only required for patients receiving treatment under Schedule A.

APPENDIX B -- SCHEDULES A AND B FOR STUDY DOSING

Schedule A	Decitabine will be administered SQ daily for 3 consecutive days (Day 1 to 3) every 28 days. The dose will be 20 mg/m^2/day. One course will be considered 28 days.
Schedule B	Decitabine will be administered SQ every 7 days for 21 days (Day 1, 8, and 15) followed by 7 days without an administration of decitabine The dose will be 20 mg/m^2/day. One course will be considered 28 days

APPENDIX C -- OPERATING CHARACTERISTICS OF ADAPTIVE RANDOMIZATION

	Schedule A	Schedule B
OR Rate	0.1	0.1
Expected # of Patients	34	35
Pr (Select)	0.094	0.095
Pr (Select Early)	0.094	0.095
Pr (Stop Early)	0.21	0.21
OR Rate	0.05	0.2
Expected # of Patients	26	51
Pr (Select)	0.002	0.69
Pr (Select Early)	0.002	0.68
Pr (Stop Early)	0.79	0.02
OR Rate	0.1	0.2
Expected # of Patients	30	47
Pr (Select)	0.01	0.47
Pr (Select Early)	0.01	0.46
Pr (Stop Early)	0.5	0.03
OR Rate	0.2	0.2
Expected # of Patients	37	37
Pr (Select)	0.12	0.14
Pr (Select Early)	0.11	0.14
Pr (Stop Early)	0.14	0.12
OR Rate	0.2	0.3
Expected # of Patients	32	47
Pr(Select)	0.02	0.42
Pr(Select Early)	0.02	0.41
Pr(Stop Early)	0.42	0.03
OR Rate	0.1	0.3
Expected # of Patients	25	54
Pr (Select)	0.0008	0.80
Pr (Select Early)	0.0008	0.80
Pr (Stop Early)	0.81	0.002

*Remark: Pr (Inconclusive) = 1 – Pr(schedule A selected) – Pr (schedule B selected)

APPENDIX D – PROPOSED MODIFIED INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR ALTERING NATURAL HISTORY OF MDS

Category	Response criteria (responses must last at least 4 weeks)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ Hgb ≥ 11 g/dL; Platelets ≥ 100 X 10^9/L; Neutrophils ≥ 1.0 X 10^9/L†; Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment† Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5%-10% blasts: ≥ 50% increase to > 10% blasts 10%-20% blasts: ≥ 50% increase to > 20% blasts 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
*Dysplastic changes should consider the normal range of dysplastic changes (modification).
†Modification to IWG response criteria.
‡In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy cycles should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.
(From *Cheson et al., 2006*)

APPENDIX E – PROPOSED MODIFIED INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR HEMATOLOGIC IMPROVEMENT

Hematologic improvement*	**Response criteria (responses must last at least 8 weeks)**
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100 X 10^9/L)	Absolute increase of ≥ 30 X 10^9/L for patients starting with > 20 X 10^9/L platelets Increase from < 20 X 10^9/L to > 20 X 10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0 X 10^9/L)	At least 100% increase and an absolute increase > 0.5 X 10^9/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

Deletions to the IWG response criteria are not shown.
To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).
†Modification to IWG response criteria.
‡In the absence of another explanation, such as acute infection, repeated cycles of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.
(From *Cheson et al., 2006*)

APPENDIX F - SUMMARY OF CHANGES

Section	Original Protocol Text	Amendment 1 Text	Justification of Change
Title Page	RANDOMIZED OPEN-LABEL PHASE 4 STUDY OF LOW DOSE DACOGEN® FOR INJECTION (DECITABINE) IN PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES	RANDOMIZED OPEN-LABEL PHASE 2 STUDY OF LOW DOSE DACOGEN® FOR INJECTION (DECITABINE) IN PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES	Title of the study was changed throughout to better reflect the study design as a Phase 2 trial.
Synopsis/ Trial design	This study will be conducted at up to 6 study centers in the United States.	This study will be conducted at approximately 6 study centers in the United States.	Wording change to allow more flexibility in the number of study centers.
1. Introduction	A recent analysis by Garcia-Manero, et al, of the prognosis of patients with lower risk MDS (in the Low and Int-1 subgroup) was performed using data from patients referred to the M. D. Anderson Cancer Center from 1976-2005 (*Shan et al. 2007*).	A recent analysis by Garcia-Manero, et al, of the prognosis of patients with lower risk MDS (in the Low and Int-1 subgroup) was performed using data from patients referred to the M. D. Anderson Cancer Center from 1976-2005 (*Garcia-Manero et al. 2008*).	The reference was changed to correct a previous error.
3. Study Design	This randomized Phase 4, open-label, efficacy and safety study will evaluate patients with lower risk MDS in two different SQ administration schedules of decitabine.	This randomized Phase 2, open-label, efficacy and safety study will evaluate patients with lower risk MDS in two different SQ administration schedules of decitabine.	The phase designation of the study was changed throughout to better reflect the study design as a Phase 2 trial.
3.1 Rationale for Dose and Administration Methods Used	In a recent study of decitabine (Kantarjian et al., 2007), administration every 28 days was safe and associated with clinical activity. Investigators at M. D. Anderson Cancer Center, in an analysis of the molecular effects of decitabine in patients treated in clinical studies, have suggested potentially more effective schedules of hypomethylation induction (Shan et al., 2007).	In a recent study of decitabine (*Kantarjian et al., 2007*), administration every 28 days was safe and associated with clinical activity. Investigators at M. D. Anderson Cancer Center, in an analysis of the molecular effects of decitabine in patients treated in clinical studies, have suggested potentially more effective schedules of hypomethylation induction (*Kantarjian et al., 2007*).	The reference was changed to correct a previous error.

Section	Original Protocol Text	Amendment 1 Text	Justification of Change
3.2 Study Duration and Dates	Patients will receive the first course of therapy without interruption regardless of degree of myelosuppression.	Patients will receive the second course of therapy without interruption regardless of degree of myelosuppression.	This is a clarification to acknowledge that, although myelosuppression may occur in the first cycle., the second cycle should not be interrupted.
3.2.1 Patient Dose Modification	If prolonged myelosuppression (≥42 days) is observed (see Section 5.1), decitabine will be administered at the next lower dose level as shown in Table 3-1.	If prolonged myelosuppression (≥42 days) is observed after cycle 1 (see Section 5.1), decitabine will be administered at the next lower dose level as shown in Table 3 1.	The text was changed to ensaure that the cycle 1 dose was not changed and that changes would be permitted in subsequent cycles.
5.1 Treatments Administered	Due to the volume of drug that may be needed by some patients, at the discretion of the investigator, dosing may be done in one or multiple injections, given during the same drug administration session(s).	Due to the volume of drug that may be needed by some patients, at the discretion of the investigator, dosing may be done in one or multiple injections, given during the same drug administration session(s), particularly if the volume is > 2mL.	This change clarified when multiple injections should be considered.
5.1 Treatments Administered	Patients will receive the first course of therapy without interruption regardless of degree of myelosuppression. Patients can continue to receive therapy, as described in Section 3.2, as long as the investigator feels that patient is benefiting, or might benefit, from decitabine (see below). After the first course of therapy, at the discretion of the treating physician, the interval between the cycles of therapy can be spaced out ± 3 days. However, within each cycle the schedule of study events should be followed as closely as possible.	Patients will receive the second course of therapy without interruption regardless of degree of myelosuppression. Patients can continue to receive therapy, as described in Section 3.2, as long as the investigator feels that patient is benefiting, or might benefit, from decitabine (see below). After the first course of therapy, at the discretion of the treating physician, the interval between the subsequent cycles of therapy can be spaced out ± 3 days. However, within each cycle the schedule of study events should be followed as closely as possible.	This was to ensure that the first cycle was completed as closely as possible to the procedures specified in the protocol and that spacing of cycles occurred only after the first cycle was completed

Section	Original Protocol Text	Amendment 1 Text	Justification of Change
5.1 Drug Administration	If prolonged myelosuppression (≥ 42 days) is observed (defined by an absolute neutrophil count [ANC] of < 1 x109/L and a platelet count of < 30 x109/L), then subsequent cycles of decitabine will be given at the next lower dose (see Table 3 1), once the counts recover.	If prolonged myelosuppression (≥ 42 days) is observed after cycle 1 (defined by an absolute neutrophil count [ANC] of < 1 x109/L and a platelet count of < 30 x109/L), then subsequent cycles of decitabine will be given at the next lower dose (see Table 3 1), once the counts recover.	This text was changed to ensure that changes in dosing would not be made in cycle 1.
5.9 Study Drug Administration	For patients who require a large volume of drug be administered, multiple injections during the same administration session are permitted at the discretion of the investigator.	For patients who require a large volume (i.e., > 2mL) of drug be administered, multiple injections during the same administration session are permitted at the discretion of the investigator.	As described earlier, this change was made to guide the investigator on when multiple injections should be considered.
6.3.1. Cycle 1 Only	Occurring on Day 1 only: • Physical Exam • ECOG Performance Status • Body weight Occurring throughout the cycle: • Body Weight Day 2, 3, 8 and 15 (Day 2 and 3 are only for those patients receiving treatment under Schedule A; Day 8 and 15 are only for those patients receiving treatment under Schedule B). • Vital signs Day 1, 8, 15, and 22.	Occurring on Day 1 only: • Physical Exam • ECOG Performance Status Occurring throughout the cycle: • Body Weight Day 2, 3, 8 and 15 (Day 2 and 3 are only for those patients receiving treatment under Schedule A; Day 8 and 15 are only for those patients receiving treatment under Schedule B). • Vital signs Day 1,2, 3, 8, 15, and 22 (Day 2 and 3 are only for those patients receiving treatment under Schedule A). Vital signs should be obtained prior to study drug administration.	Additional timepoints and clarification around the timing and collection of both body weight and vital signs were added in this amendment.
6.3.2 For All Subsequent Cycles	<<New Text added in the Amendment>>	Occurring throughout the cycle: • Body Weight per dosing schedule. • Vital signs at all visits (to be obtained before study drug administration).	This continues the clarification and addition timepoints and collection details for assessments of body weight and vital signs in subsequent cycles.

Section	Original Protocol Text	Amendment 1 Text	Justification of Change
6.7.2.1 Reporting Requirements	Safety contact information is: Sandra Fielder, MD Telephone: 952-406-3197 Fax #: +1 952 346 4940 Phone: 1-800-562-5580 E-mail: drugsafety@mgipharma.com	MGI Global Drug Safety and Pharmacovigilance contact information is: Sandra Fielder, MD Telephone: 952-406-3197 Pam Johnson, Pharm.D. Telephone: 952- 406-3185 Fax #: +1 952 346 4940 Phone: 1-800-562-5580 E-mail: drugsafety@mgipharma.com	An additional safety contact name and number was added and the general language and phone number was changed to reflect internal departmental changes occuring since the original protocol was finalized.
7.2.4.1.2 Primary Analysis	Patients must be on treatment for at least 3 months in order to be eligible for evaluation of response status.	Patients must be on treatment for at least 3 cycles in order to be eligible for evaluation of response status.	This text was changed to put all of the vital timepoints into cycle times for consistency across all patients.
10. References	**Deleted text:** Shan J, Kantarjian H, Pierce S, Estey E, Garcia-Manero G. A new prognostic score for patients with lower-risk myelodysplastic syndrome (MDS) allows the identification of a subset of patients with poor prognosis. Blood 2007:375s, Abstract #7076.	**New Text added in this amendment:** Garcia-Manero, G, Shan, J, Faderl, S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. *Leukemia* 2008;22(3):538-543.	This change was made to correct a prior reference error.
Appendix A – Schedule of Study Events	A redline corrected version of the schedule of study events is provided in the following pages.	The redline shows the addition of new text and timepoints clarifying changes in timing of assessments and to ensure that cycle 1 is conducted per the protocol amendment instructions. Additional procedure flexibility is provided for subsequent cycles.	

APPENDIX A – SCHEDULE OF TRIAL PROCEDURES FOR DACO-026

		Cycle 1								Cycle 2 (±3 Days) through End of Treatment							
	Screening[b]	Day 1	Day 2	Day 3	Day 5	Day 8	Day 15	Day 22	Day 28	Day 1	Day 2	Day 3	Day 8	Day 15	Day 22	Day 28	Termination[k]
Informed Consent[a]	X																
Inclusion/Exclusion Criteria	X																
Medical History	X																
Concomitant Medications/ Transfusions[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X								X							X
Pregnancy Test	X																
Perform IPSS assessment of disease	X																
ECOG performance status	X	X								X							X
Body Weight[d]	X	X	A	A		B	B			X	A	A	B	B			X
Vital Signs	X	X	X[l]	X[l]		X	X	X		X			X	X	X		X
Hematology[e]	X	X				X	X	X		X			X	X	X		X
Blood Chemistry[f]	X	X				X	X	X		X			X	X	X		X
Randomization	X																
Drug Administration[g]		A/B	A	A		B	B			A/B	A	A	B	B			
Cytogenetics[h]	X														7 days prior to start of next cycle		X
Bone Marrow Aspirate[j] (Please see Notes, next page, for timing)	X														7 days prior to start of next cycle		X
Peripheral Blood Sampling for Molecular Correlative Study (optional)[i]	X	A/B		A/B	A	A/B	A/B	A/B		X			X	X	X		X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

All Table Notes Next Page. Shaded area above is Cycle 1

Note: The chart above outlines the study procedures required at each visit. One cycle is considered 28 days

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Table Notes:

a No study assessments beyond those specified as screening assessments will be performed without obtaining written informed consent.

b The pre-study procedures may be performed within 14 days prior to Randomization.

c Concomitant Medications include transfusions

d Body weight assessed for all patients at Screening, all Cycles Day 1, and Termination. Body weight also assessed per dosing Schedule [Schedule A=Cycle Day 2 and 3, Schedule B=Cycle Day 8 and 15].

e Hematology- All samples will be obtained after drug administration except for screening, when possible.

f Blood Chemistry - All samples will be obtained after drug administration except for screening, when possible.

g Study drug administration will follow one of two schedules:

Schedule A, decitabine is given 20 mg/m2 daily SQ for three consecutive days (days 1, 2, 3) every 28 days;

Schedule B, decitabine is given 20 mg/m2 daily SQ once every seven days (days 1, 8, 15) for 3 consecutive weeks with one week of rest between cycles.

Patients may continue on therapy until they are no longer deriving clinical benefit from therapy. Each SQ injection will be administered at one of several suitable anatomic sites (e.g., abdomen, thigh, upper arm) on a rotating basis. Record the time of drug preparation along with the time and site of drug administration.

h Cytogenetics will be performed at screening and in tandem with the bone marrow assessments during the study and at study discontinuation, as described below. Patients are not required to undergo cytogenetics if they have had a documented clinically indicated assessment within 4 weeks before study discontinuation.

i The pre-study bone marrow aspirate sampling may be performed up to 28 days prior to first dose of study dose. Bone marrow aspirates in cycle 2, 3 and then every subsequent 3rd cycle must be obtained within 7 days prior to the start of the next cycle. If patients have a documented complete remission, an additional bone marrow aspirates must be performed at the end of the next cycle after initial documentation of CR. After this, patients with CR are not required to have additional bone marrow assessments until clinically indicated. Patients are not required to have a bone marrow assessment if they have had a documented assessment within 4 weeks before study discontinuation.

j Peripheral Blood for optional Molecular Correlative study will be collected based on the Randomization schedule during the 1st cycle: After the 1st cycle, peripheral blood for the Molecular Correlative study will be obtained prior to each course of therapy and weekly thereafter as shown in Table 6-1 and Table 6-2

k End of treatment/end of study assessments include adverse events, concomitant medications, including transfusions, physical exam, including weight, vital signs and assessment of ECOG performance status. Laboratory studies including CBC with differential (absolute values) and platelets. (Peripheral blasts should be assessed) Serum chemistries, including bicarbonate, calcium, glucose, BUN, potassium, chloride, sodium, creatinine, total bilirubin, AST, ALT, and alkaline phosphatase. Bone marrow aspirate assessment for morphology and cytogenetics. Peripheral blood smear and aspirate are to be sent to M.D. Anderson for processing and review.

l Vital Sign recording for Day 2 and 3 are only required for patients receiving treatment under Schedule A.

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PROTOCOL SIGNATURE PAGE

DACO-026
PROTOCOL AMENDMENT 1
RANDOMIZED OPEN-LABEL PHASE 2 STUDY OF LOW DOSE DACOGEN® FOR INJECTION (DECITABINE) IN PATIENTS WITH LOW OR INTERMEDIATE 1 RISK MYELODYSPLASTIC SYNDROMES

I confirm that the appropriate member(s) of my staff and I have read, understand, and will conduct the study according to this protocol and consistent with the ICH Good Clinical Practice Guidance (ICH-E6) that have their origins in the Declaration of Helsinki or to the applicable laws and regulations of the country of the study site for which I am, whichever provides the greater protection of the individual.

I understand that the information contained in this protocol is privileged and confidential.

I understand that I am responsible for promptly providing this information to the ethics review board responsible for overseeing studies at my site and for keeping this board updated as to the progress of the study or any unexpected safety issues. Further, except to the extent necessary to obtain informed consent, I understand that information in this protocol may not be disclosed unless such disclosure is required by governmental law or local regulations. Persons to whom the information is disclosed must be apprised that the information is confidential and may not be further discussed by them. I will accept the monitor's overseeing of the study.

SIGNATURES OF AGREEMENT:

Investigator	Date
Emile Youssef, M.D., Ph.D. Medical Director Medical & Scientific Affairs Eisai Inc., Oncology Business Unit 100 Tice Boulevard Woodcliff Lake, NJ 07677 Telephone # 201-746-2290, Fax # 201-746-2288	5/1/08 Date