

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-794

Medical Review(s)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ONCOLOGIC DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW -

ADDENDUM

NDA: 50-794 N-000; N-000 BM; N-000 BM
IND: 64,251 N-043; N-046
Letter Date: December 26, 2003.
Stamp Date: December 29, 2003; February 23, 2004; March 23, 2004; April 22, 2004
Established Name: Azacitidine; 5-azacytidine
Chemical name: 4-amino-1- β -D-ribofuranosyl-1,3,5-triazin-2(1H)-one
Proposed Trade Name: Vidaza™
Pharmacologic category: Antimetabolite, inhibitor of DNA methyltransferase and of uridine kinase

Formulation: Each vial contains 100 mg of 5-Azacytidine as powder and 100 mg mannitol as powder, to be dissolved in 4 mL of sterile water
Dosing Regimen: 75 mg/m²/day for 7 days every 28 days
Route of administration: Subcutaneous

Indication: Myelodysplastic syndromes, all subtypes
Intended Population: Patients with high-risk myelodysplastic syndromes

Sponsor: Pharmion Corporation, Boulder, CO
Priority Designation: P

Medical reviewer: Edvardas Kaminskas, M.D.
Medical Team leader: Ann Farrell, M.D.
Statistical reviewer: Yong-Cheng Wang, Ph.D.
Clinical Pharmacology/Biopharmaceutics reviewer: Sophia Abraham, Ph.D.
Pharmacology/Toxicology reviewer: Shwu-Luan Lee, Ph.D.
Chemistry reviewer: Li-Shan Hsieh, Ph.D.
Project Manager: Ms. Amy Baird

Date review completed: May 19, 2004
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This Addendum to Medical Officer's Review is part of the review filed in DFS on April 26, 2004.

XI. APPENDIX (Continued)

4. Additional Analyses of the Initial Positive Effect to Azacitidine in Responders in CALGB 9221, 8921 and 8421 Clinical Trials

The initial positive effect, as defined by the sponsor and not described in the CALGB protocols, was the first day of achievement of target for ≥ 4 weeks for at least 1 abnormality at baseline. The data below are compiled by the reviewer from sponsor's Integrated Summary of Efficacy Tables 10, 11, 37 and 63 for the purpose of 1) identifying the length of treatment time for initial positive effect to become evident, and 2) the types of initial positive effects and the length of time for these effects to become manifest.

Reviewer's Table. Day and Cycle Number of the Initial Positive Effect, Number of Responders, and Cumulative Percent of Responders in All Azacitidine-Treated Subjects in CALGB 9221, 8921 and 8421 Trials

Cycle Number (days)	CALGB Trial and Day of the Initial Positive Effect	Number of Responders	Cumulative number (%)
1 (28 days)	CALGB 9221: 29, 31, 33, 36, 36	5	19 (46%)
	CALGB 8921: 15, 15, 17, 22, 24, 30, 32	7	
	CALGB 8421: 8, 9, 9, 11, 15, 23, 29	7	
2 (56 days)	CALGB 9221: 55, 57, 57, 57, 58, 63, 68	7	31 (76%)
	CALGB 8921: 52, 57, 57	3	
	CALGB 8421: 57, 64	2	
3 (84 days)	84	1	32 (78%)
4 (112 days)	113, 113, 114, 114, 125	5	37 (88%)
5 (140 days)	141	1	38 (93%)
6 (168 days)	164	1	39 (95%)
7 (196 days)	197	1	40 (98%)
17 (476 days)	477	1	41 (100%)

Reviewer's Table. Type of Initial Positive Effect and Number of Responders with Each Type of Initial Effect

Cycle Number, Trial Number	Decrease in Blasts	Increase in Platelets	Increase in WBC	Increase in Hgb
1 CALGB 9221	0	3	2	0
CALGB 8921	5	1	1	0
CALGB 8421	7	0	0	0
2 CALGB 9221	5	1	0	1
CALGB 8921	3	0	0	0
CALGB 8421	2*	1*	0	0
3 CALGB 9221	0	1	0	0
4 CALGB 9221	2	0	0	3
5 CALGB 9221	0	1	0	0
6 CALGB 9221	0	0	0	1
7 CALGB 9221	0	0	0	1
17 CALGB 9221	0	0	1	0
Total	24	8	4	6

*One responder had a decrease in blasts and an increase in platelets in the 2nd cycle.

Reviewer's Comment:

- In CALGB 9221 82% of patients had an initial positive effect by cycle 4 and 91%, by cycle 6 (page 52 of the NDA Clinical Review). Data from all three trials show that >90% of patients had an initial positive effect by cycle 5. Only single patients responded in subsequent cycles.
- All (100%) of the initial positive effects in CALGB 8921 and 8421 trials occurred after the first two cycles, while in CALGB 9221 trial, the initial positive effects occurred in only 55% of responders during that period of time.
- Decreases in blasts was the initial positive effect 16 of 19 responders (84%) (in one response there was an increase in platelets as well) in CALGB 8921 and 8421 trials. In contrast, decreases in blasts as the initial positive effect occurred in only 7 of 22 responders (32%) in CALGB 9221 trial.
- The above results may be explained in part by differences in MDS subtypes enrolled in the three trials. Eighteen of the 19 responders in CALGB 8921 and 8421 trials had RAEB or RAEB-T, one had CMMoL. There were no RA or RARS patients in these trials. In CALGB 9221, 13 of 22 responders had RAEB or RAEB-T, 2 had CMMoL, and 7 had RA or RARS.

5. Analysis of Transfusion-Dependent and Transfusion-Independent Responders in the Three Trials

The data for this analysis are in Patient Profiles (Efficacy Parameters).

Reviewer's Table. Transfusion-Dependent Responders who Became Transfusion-Independent (Numbers of Patients)

Response	CALGB 9221	CALGB 8921	CALGB 8421	Total
CR	7	1	3	11
PR	9	2	6	17
CR + PR	16	3	9	28

Reviewer's Table. Numbers of Responders Who Were Not Transfusion-Dependent

Response	CALGB 9221	CALGB 8921	CALGB 8421	Total
CR	1	2	0	3
PR	3	2	0	5
CR + PR	4	4	0	8

cc:

NDA 50-794

HFD-150/Division File

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/s/

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List of Abbreviations

AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BSA	body surface area
BUN	blood urea nitrogen
CALGB	Cancer and Leukemia Group B
CBC	complete blood count
CI	confidence interval
CMMoL	chronic myelomonocytic leukemia (a type of MDS)
CR	complete response
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
eCRF	electronic case report form
FAB	French-American-British
G-CSF	granulocyte stimulating factor
GM-CSF	granulocyte colony stimulating factor
Hgb	hemoglobin
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
LAP	leukocyte alkaline phosphatase
LDH	lactate dehydrogenase
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
OR	odds reduction
PR	partial response
PRBC	packed red blood cells
QOL	quality of life
RA	refractory anemia (a type of MDS)
RAEB	refractory anemia with excess blasts (a type of MDS)
RAEB-T	RAEB in transformation (a type of MDS)
RARS	refractory anemia with ringed sideroblasts (a type of MDS)
RBC	red blood cell
RRR	relative risk reduction
SAE(s)	serious adverse event(s)
SC	subcutaneous
TEAE	treatment-emergent adverse event
ULN	upper limit of normal range
WBC	white blood cell

Executive Summary

I. Recommendations

A. Recommendations on Approvability

1. Approval of azacitidine for treatment of all subtypes of MDS. Azacitidine is an antimetabolite and a DNA hypomethylating agent that is effective in about 15% 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. Azacitidine treatment has not been shown to result in survival benefit (the controlled trial was not designed to test survival benefit and was not powered for this endpoint). The goals of azacitidine treatment should be to restore normal blood cell counts and normal bone marrow blast percentages, to eliminate transfusion dependence, and to decrease the risk of hemorrhage and infection. Patients with all subtypes of MDS respond to azacitidine. From a clinical perspective, I recommend regular approval of azacitidine for treatment of all subtypes of MDS.
2. The dose of azacitidine is 75 mg/m²/day SC for 7 days every 28 days. The dose is adjusted according to blood cell counts. Patients should be treated for a minimum of four (4) 28-day cycles. By that time most patients who respond will have evidence of a positive effect, which may consist of a decrease in blasts, increase in platelets or WBC, or of decrease in platelet or PRBC transfusion frequencies. Complete or partial response may require longer treatment. Treatment may be continued for as long as the patient continues to benefit.
3. Reviewer's recommendations for azacitidine (Vidaza™) labeling are incorporated into the product label.

B. Recommendations on Phase 4 Studies and/or Risk Management Steps

The sponsor should evaluate in the post-marketing phase

- Metabolism of azacitidine, in particular whether any of the cytochrome P450 enzymes is involved in the biotransformation of azacitidine
- Pharmacokinetics and safety of azacitidine in patients with mild hepatic impairment, and
- Pharmacokinetics and safety of azacitidine in patients with mild to moderate renal impairment.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Background on 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 or “smoldering” leukemia, as well as “refractory anemia” and “ring sideroblast anemia”. The classification of MDS in the trials described in this NDA is the FAB (French-American-British) classification, which was the standard for over two decades and was the current classification during the time of the trials.

The five subtypes of MDS in the FAB classification are refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). RA and RARS are mainly refractory anemias managed with transfusions. RAEB and RAEB-T have all cell lines affected and tend to transform to acute myelogenous leukemia (AML). The difference between RAEB, RAEB-T and AML is the percentage of blasts in the marrow. CMML has excess monocytes in the marrow and peripheral blood. Most MDS patients die from bleeding (because of thrombocytopenia) or infection (because of neutropenia).

Treatment of MDS. The mainstay of therapy is supportive care, including the use of RBC or platelet transfusions, and treatment with growth factors (erythropoietin, G-CSF). Cytokine therapy has not been shown to alter the natural history of disease. There is no single agent or combination therapy that is standard first-line treatment for MDS. Neither high dose therapy for AML nor treatment with low dose cytosine arabinoside have been efficacious. Hematopoietic stem cell transplantation is generally restricted to patients <60 years of age, and inappropriate for many MDS patients because their age and significant treatment-related morbidity and mortality.

Azacitidine in Treatment of MDS. Azacitidine has been used in 7 non-CALGB (Cancer and Leukemia Group B) studies, 6 of them using the same regimen that was used in the 3 CALGB trials described in this NDA. These studies were single-arm studies and had treated between 6 and 92 MDS patients. Up to 61% of patients responded to the drug. The largest numbers of patients were treated in the 3 CALGB studies, which form the clinical basis of this NDA.

B. Efficacy

Efficacy of azacitidine is demonstrated in CALGB trials 9221, 8921 and 8421. CALGB 9221 was a controlled study, in which 99 subjects were randomized to treatment with azacitidine (administered SC at a dose of 75 mg/m²/day for 7 days every 28 days) and 92 subjects were randomized to observation only. Study subjects included patients with all 5 MDS subtypes. Randomization criteria included stratification by MDS subtype. Observation only subjects were permitted to cross over to treatment with azacitidine, if they met pre-specified criteria of transfusion dependence, thrombocytopenia or neutropenia after 2 (thrombocytopenia or neutropenia) to 4 (anemia or trilineage decreases) treatment cycles. Fifty-one of the subjects in the observation arm crossed over to azacitidine treatment. CALGB 8921 enrolled 72 subjects with RAEB, RAEB-T and CMMoL, who were treated with the above regimen of azacitidine administered SC. CALGB 8421 enrolled 48 subjects with RAEB and RAEB-T, who were treated with the above dose of azacitidine, which was administered IV. CALGB central laboratory adjudicated the following number of subjects to have AML at study entry: 19 subjects in study 9221 (10 in the azacitidine treatment arm and 9 in the observation only arm), 17 subjects in study 8921, and 1 subject in study 8421.

The primary efficacy endpoint was the overall response rate (complete and partial response rates). Complete response was defined as normalization of peripheral blood counts and bone marrow blast percentages for at least 4 weeks. Partial response was defined as $\geq 50\%$ restoration in deficit from normal levels of baseline blood counts and absence of myeloblasts in peripheral blood, and $\geq 50\%$ decrease in myeloblasts in marrow from baseline (except in RA and RARS, in which there is no increase in marrow myeloblasts). In study 9221, the response rates were 15.7% in subjects randomized to azacitidine treatment and 0% in observation only subjects. The response rate was 12.8% in azacitidine after observation crossover subjects. The response rate was 13.9% in study 8921 and 18.8% in study 8421. Subjects adjudicated to have AML at study entry had the same response rate as MDS subjects. The response rate to azacitidine in the 3 studies, with or without the subjects adjudicated to have AML at study entry, was 15.2%.

The responses were long lasting in most patients. The duration of responses could not be accurately estimated, because over 70% of subjects remained in response status at the time of withdrawal from the trials. Subjects with complete and partial responses lost transfusion dependence. In addition to complete or partial responses, azacitidine treatment resulted in lesser responses, termed "Improvement" that occurred in about 16% of subjects in the 3 trials, and consisted of increased blood counts and loss of transfusion dependence. The median duration of improvement was 195 days.

The controlled trial was not powered to detect differences in survival between azacitidine-treated and observation only patients. Moreover, crossover of observation subjects to azacitidine treatment made the two groups not comparable.

C. Safety

- The safety profile is based on adverse event data in 220 subjects in the 3 CALGB trials and in 6 subjects in a clinical pharmacology study.
- In these trials azacitidine was used to treat MDS, a condition that in its pathophysiology overlaps to a great extent the most common toxicities of azacitidine. Therefore, it is often difficult to distinguish azacitidine toxicity from progression of MDS.
- The same dose of azacitidine was used in the 3 clinical trials. The drug was administered SC in the controlled trial and one uncontrolled trial, and IV in the other uncontrolled trial. The extent of exposure was similar in the 3 trials.
- The most frequent reason for withdrawal from the trials was no response to azacitidine, followed by development of AML, adverse event, decision not to continue, other reasons and death.
- There were no deaths attributed to azacitidine.
- Serious adverse events occurred in about 60% of azacitidine-treated subjects and in about 36% of observation only subjects. The most common serious adverse events resulting in hospitalization were thrombocytopenia, febrile neutropenia, fever and pneumonia.
- Over 99% of subjects in the azacitidine treatment groups and over 96% of subjects in the observation only group reported adverse events. There were more subjects reporting gastrointestinal events (nausea, vomiting, diarrhea, constipation, and anorexia), hematologic events (neutropenia, fever, rigors, ecchymoses, ptechia, epistaxis), injection site events, cough, dyspnea, arthralgia, headache, weakness, dizziness and insomnia among azacitidine-treated subjects than among observation only subjects. After correction for mean duration of exposure, there were more observation only subjects with anemia and thrombocytopenia, and there were more azacitidine-treated subjects with gastrointestinal adverse events.
- The highest proportion of subjects with adverse events was in the first two cycles of azacitidine therapy; this proportion declined markedly in subsequent cycles.
- The most common reasons for azacitidine discontinuation, dose reduction or therapy interruption (beside lack of effectiveness) were neutropenia, leukopenia and thrombocytopenia.
- Concomitant medications to treat adverse events were administered to 95% of azacitidine-treated patients (for gastrointestinal symptoms and fever) and to 73% of observation only patients (for fever, hypokalemia and nausea).
- Blood cell counts were low at baseline in all subjects and decreased further in subjects treated with azacitidine. Blood counts increased in subjects who showed a response or improvement.
- Liver function abnormalities occurred in about 16% of subjects treated with azacitidine and in 8% of observation only subjects. These abnormalities coincided with intercurrent illnesses, including hepatobiliary disorders. Three

patients developed hepatic impairment during treatment with azacitidine, two of them had previously diagnosed cirrhosis.

- Renal adverse events were rare, transient and attributed to concomitant conditions. Five azacitidine-treated patients and one observation only patient developed renal failure in a variety of settings, such as sepsis, hypotension, hypertension, diabetes mellitus and heart failure.
- Gastrointestinal adverse events tended to increase with azacitidine dose. Most other types of adverse events were not dose-related.
- Some adverse events were more frequently reported by females than males. These were vomiting, diarrhea, headache, injection site erythema, arthralgia, tachycardia, and post-procedural hemorrhage. Thrombocytopenia was more frequently reported by males than by females.
- There was no relationship between the subjects' age and the proportion of subjects with adverse events.
- A limitation of this safety evaluation is that the data have been re-collected by the sponsor from hospital records and not from original CRFs.
- Azacitidine appears to be a relatively safe drug for a pre-malignant or malignant condition such as MDS. Azacitidine-related adverse events appear to be relatively easily controlled with concomitant medications and blood product use.

D. Dosing

The recommended starting dose is 75 mg/m²/day subcutaneously for 7 days every 28 days. This is the dose used in the controlled study and in one single-arm study. The second single-arm study used the same dose administered intravenously. The starting dose may be increased to 100 mg/m²/day if no beneficial effect is seen after 2 treatment cycles. The starting dose is not adjusted for decreased renal or hepatic function. Subsequent doses are reduced for leukopenia, neutropenia, thrombocytopenia, and reduced renal function.

E. Special Populations

1. Gender differences in pharmacology/safety/effectiveness. There appear to be no gender differences in efficacy of azacitidine. Reviewer's Table below presents the gender analysis for complete and partial responses (CR + PR) in the three studies.

Reviewer's Table. Gender Analysis for Efficacy (CR + PR), All Azacitidine-Treated Patients

Gender	CALGB 9221	CALGB 8921	CALGB 8421	Total
Male	15/103 (14.6%)	6/49 (12.2%)	5/31 (16.1%)	26/183 (14.2%)
Female	7/47 (14.9%)	4/23 (17.4%)	4/17 (23.5%)	15/87 (17.2%)

In safety analysis, female subjects tended to have a higher frequency of some adverse events than male subjects, such as vomiting, diarrhea, headache, injection site erythema, arthralgia, tachycardia, and post-procedural hemorrhage. More male subjects had thrombocytopenia.

2. Ethnic/racial differences. Analysis of results by ethnic or racial background was not possible, because >95% of subjects were White (Caucasian).
3. Issues with the elderly. Response rates were similar across age groups, as shown in the Reviewer's Table below.

Reviewer's Table. Response Rates (CR + PR) By Age Groups, All Azacitidine-Treated Patients

Age Group	CALGB 9221	CALGB 8921	CALGB 8421	Total
<65 years	6/53 (11.3%)	3/26 (11.5%)	6/21 (28.6%)	15/100 (15.0%)
65 – 74 years	12/61 (19.7%)	5/30 (16.7%)	2/24 (8.3%)	19/115 (16.5%)
≥75 years	4/36 (11.1%)	2/16 (12.5%)	1/3 (33.3%)	7/55 (12.7%)

Safety analysis showed that the frequencies of treatment related adverse events did not increase with age, except for neutropenia, which was more frequent in the >65 year-old group than in the <65 year-old group. There were higher frequencies of pharyngitis, injection site erythema and pain, nightsweats, and hematomas in the <65 year-old group than in the >65 year-old group.

4. Patients with renal impairment and hepatic impairment. Patients with hepatic or renal impairment were excluded from the studies. About 16% of azacitidine-treated subjects had hepatic adverse events compared to about 8% of observation only subjects. (N.B. Exposure time was twice as long in azacitidine treatment group as in observation only group). Most of the adverse events were complications of intercurrent hepatobiliary illnesses. However, three patients developed hepatic failure during treatment with azacitidine; two of the patients had previously diagnosed liver cirrhosis. About 29% of azacitidine-treated patients had renal adverse events compared to 12% of observation only subjects. Most common were dysuria, hematuria, renal impairment, and urinary frequency. Most serious adverse events in both groups were hematuria and renal failure. Five azacitidine-treated patients and one observation only patient developed renal failure in clinical settings such as sepsis, hypotension, hypertension, diabetes mellitus and heart failure.
5. Pediatric studies. The sponsor is not proposing pediatric studies. Azacitidine was designated as an Orphan Drug on December 3, 2001 (designation request #01-1501).
6. Pregnancy use information. Pregnancy Category D. The proposed label states that women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with azacitidine.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

1. Drug established name: 5-azacytidine (NSC #102816)
2. Drug trade name: Vidaza™ (azacitidine for injectable suspension)
3. Drug class: antimetabolite, inhibitor of uridine kinase and of DNA methyltransferase
4. Proposed indication: Treatment of all types of myelodysplastic syndromes
5. Dose: Dose: 75 mg/m²
6. Regimens: 75 mg/m²/day x 7 days subcutaneously (SC) every 28 days for a minimum of 4 cycles
7. Age Groups: adults

B. State of Armamentarium for Indication

1. Myelodysplastic syndromes (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 or "smoldering" leukemia, as well as "refractory anemia" and "ring sideroblast anemia". The etiology is unknown in cases of *primary MDS*; chemical or radiation injury, chemotherapy, and radiotherapy may cause *secondary MDS*. Secondary MDS generally has a poorer prognosis than primary MDS.

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, petechiae; 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.

This NDA deals with treatment of primary MDS, and MDS in the text will refer to primary MDS. Several classifications of MDS have been proposed. The most commonly accepted is the FAB (French-American-British) classification, 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 + $\geq 15\%$ 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): $\leq 20\%$ 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%.
2. Response Criteria in 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.
- 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.
 - 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).

3. Treatment of MDS. Currently there is no single agent or combination therapy that is standard first-line treatment for MDS. The mainstay of therapy is supportive care, including the use of RBC or platelet transfusions, and treatment with growth factors (erythropoietin, G-CSF). RBC transfusions and erythropoietin have been effective for the management of anemia in RA and RARS with serum erythropoietin levels <500 U/L. Treatment of neutropenia with G-CSF has not been effective in reducing infections, and has been associated with shorter overall survival of patients with RAEB. Data assessing the efficacy of growth factor therapy for thrombocytopenia are limited. Regardless of the success in correcting individual cytopenias, cytokine therapy has not been shown to alter the natural history of disease.

More aggressive therapy, such as hematopoietic stem cell transplantation, is associated with significant treatment-related morbidity and mortality and is generally restricted for patients less than 60 years of age. As a result, most MDS patients are not candidates for this therapy because of their age. For the same reason most MDS patients are not candidates for high dose chemotherapy.

4. Azacitidine in Treatment of MDS. The results of CALGB trials 9221, 8921, and 8421 form the basis of this NDA, and will be evaluated in the review. However, azacitidine has been used in 7 non-CALGB studies, 6 of them using the same regimen that was used in the CALGB trials (75 mg/m²/day x 7 every 28 days). The results of the study are summarized below.

Reviewer's Table: Supportive Literature for Use of 5-Azacitidine in MDS

Reference	Study Design	Results
Chitambar C, et. al.	Single arm, Open-Label, Dose escalation study of continuous infusion for 14 days every month in 16 MDS patients, doses studied included 10 mg/m²/day – 35 mg/m²/day	16 enrolled (11m:2f, 3 unknown), median age 64 years (range 31-76), prior history of malignancy allowed (7 prior chemo/XRT), 1 AML pt., 15 evaluable, response rate 3/15 or 20 %, all PRs, 5/15 (33%) patients became transfusion-free
Gryn J, et. al.	Single arm, Open-Label, study of subcutaneous administration of 75 mg/m² 5-azacytidine for 7 days every month in 57 MDS patients	57 enrolled (5 AML, 2 never received rx), 50 evaluable (30 m:18 f, 2 unknown), median age 71 (range 36-88), 18/50 (36%) patients became transfusion-free
Jani CR, et. al.	Case Series of 14 patients treated with subcutaneous administration of 75 mg/m² 5-azacytidine for 7 days every month	14 patients (1 t-AML), 13 evaluable, 7/13 (54%) transfusion-free
Rugo H, et. al.	Open-Label, subcutaneous administration of 75 mg/m² 5-azacytidine for 7 days for 6 months in 35 MDS patients*	35 enrolled, 26 evaluable (others too early), median age 66 (range 48-81), 38% CR+PR, 19%- improved
Rugo H, et.al.	Open-Label, subcutaneous administration of 75 mg/m² 5-azacytidine for 7 days for 6 months in 92 MDS patients*	92 enrolled, 17 not evaluable (3 too early), median age not given, 42% CR+PR, 19%-improved
Litam PP, et. al.	Case Report of 1 MDS patient with RAEBT treated with 5-azacytidine	Improvement in WBC parameters and blast percentages

Reviewer's Comments:**1. MDS types. Various investigators have questioned the term MDS, which includes**

- relatively indolent idiopathic anemias with a relatively lower frequency of progression to AML,
- clonal multilineage cytopenias, and
- oligoblastic myelogenous leukemias that often progress into overt AML,

and the FAB classification, which

- uses percentage of blasts to differentiate between types ("inconsistent with biological behavior of cancer and medicine's classification of cancer...myelogenous leukemia, not refractory anemia, is the name of the tumor whether the marrow has 8% or 80% blast cells" [Lichtman MA & Brennan JK in Williams Hematology]),
- includes chronic myelomonocytic leukemia, which can be included among chronic myelogenous leukemias, and
- fails to include syndromes such as multilineal cytopenia with hypercellular marrow, amegakaryocytic thrombocytopenia, chronic hypoplastic neutropenia, aplastic anemia with evidence of clonal hematopoiesis, paroxysmal nocturnal hemoglobinuria-aplastic anemia syndrome, and syndromes with cytogenetic abnormalities, such as the 5q syndrome and the monosomy 7 syndrome.

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 to 20%. CMMoL is now included among chronic myelogenous leukemias. Various centers have been retrospectively analyzing their patients by the original FAB System and the new WHO system (Germing U et al.; Howe RB et al.; Nosslinger T et al.; Strupp C et al.; Albitar M et al.). WHO classification has so far not been met by universal agreement. A number of authors have urged delay of its adoption.

Another classification system (International Prognosis Scoring System, IPSS) by the International MDS Study Group aims to classify MDS by prognostic factors, and less by morphological demarcation of subgroups. Clearly, the biological behaviors of MDS syndromes are at present insufficiently well understood to create a useful diagnostic and prognostic classification.

2. Prognoses of MDS types. Median survivals and transformation rates to AML for MDS types (results of a meta-analysis of six studies) are shown in the table

below (from Greenberg PL in Hematology, eds. Hoffman et al.). The vast heterogeneity of median survivals (a 15-fold difference between RARS and RAEB-T) and of transformation to AML (a ten-fold difference between RARS and RAEB-T) presents difficulties in evaluations of therapeutic interventions in MDS.

FAB subgroup	Median survival (months)	Transformation to AML	Proportion of MDS patients (%)
RA	43	15%	25%
RARS	73	5%	15%
RAEB	12	40%	35%
RAEB-T	5	50%	15%
CMMoL	20	35%	10%

C. Important Milestones in Product Development

1. The original IND (#7574) for azacitidine was submitted by NCI in February 1971 for a various antineoplastic indications. Azacitidine, alone or in combination with other chemotherapeutic drugs, was used in at least 70 clinical trials in patients with acute myelogenous leukemia, chronic myelogenous leukemia, and various solid tumors. By 1976, more than 800 cancer patients had been treated with a variety of regimens (Van Hoff et al). In addition, Ley et al. (1982) treated 5 patients with severe β -thalassemia or with homozygous sickle cell disease, who demonstrated an increase in γ -globin synthesis contributing to increased Hgb F formation. These findings suggested an effect of azacitidine on cell differentiation at doses lower than those used in treatment of AML.
2. The Upjohn Company submitted an NDA — on May 11, 1982, based on data from the NCI-sponsored studies. The sponsor received a non-approvable letter from the FDA on May 31, 1983.
3. FDA met with Pharmacia on June 19, 2000 to discuss azacitidine for approval for the treatment of patients with MDS.
4. Pharmion Corporation acquired global rights to azacitidine from Pharmacia in July 2001, and has been meeting with FDA since December 19, 2001 to have azacitidine approved for the treatment of patients with all types of MDS. The agreed-on plan is for accelerated approval on the basis of the trials submitted with this NDA, and for a confirmatory trial to be started during the NDA review, followed by a regular approval.

D. Other Relevant Information

1. FDA responded to a series of questions by Pharmion on October 3, 2002 regarding a revised investigational plan of pre- and post-approval studies necessary to characterize the bioavailability and metabolism of azacitidine. The plan included examination of the effect of demographics on PK, the effect of renal and hepatic dysfunction on PK, and of drug-drug interactions between

azacitidine and other concomitantly administered drugs. The other questions related to the pivotal CALGB trial data to be submitted with the NDA. There were issues regarding retrospective definition of primary and secondary endpoints, retrospective collection of data, missing data, crossover to treatment arm, varying number of treatment cycles per patient, quality of QOL data, and other statistical analyses. A Special Protocol Assessment of the confirmatory study plan was requested by the Agency.

2. The confirmatory trial was described in January 28, 2003 documents as an open label, randomized, comparative, controlled, multi-center trial in high-risk MDS patients. A total number of 334 high-risk MDS patients will be randomized to receive either azacitidine 75mg/m²/day x 7 days every 28 days or "Standard of Care", consisting of three treatment options at the discretion of the treating physician. The primary endpoint will be survival. The secondary endpoints will be rates of transfusion, infections, and hemorrhage, and of transformation to AML or death.
3. Since MDS is a serious life-threatening disease for which there is no other specific therapeutic agent, azacitidine is a potential candidate for accelerated approval under 21 CFR Part 314, Subpart H. FDA requested a submission of an interim analysis of the Phase 4 confirmatory trial that shows a favorable effect on agreed-on secondary endpoints and that provides assurance of trial completion in an acceptable time frame (correspondence dated March 21, 2003).
4. A pre-NDA meeting was held with the sponsor on April 14, 2003. The main issues are summarized as follows:
 - The FDA had previously stated that the proposed NDA data package centered primarily around CALGB study 9221 might provide an adequate basis for accelerated approval, provided that the confirmatory study is initiated prior to submitting the NDA. However, it has since become apparent that the results of study 9221 are poorly documented, and that a successful interim analysis of agreed upon surrogate endpoint(s) from the confirmatory study is needed for accelerated approval.
 - Evidence (especially peripheral blood and bone marrow slides) of diagnosis of MDS at baseline and responses to treatment were not found for a large proportion of study subjects. The Principal Investigators in CALGB 9221 could not be identified at a substantial proportion of participating institutions despite the best efforts of Pharmion, NCI and CALGB. The CALGB studies were conducted under IND #7574 and funded by NCI and FDA. CALGB policy is to destroy regulatory documentation after 3 years. Pharmion proposed to provide two lists of investigators, the original principal investigators for the original trials and the "responsible physicians" at the time of data re-collection, and will review these listings against the available disqualification /restricted/ assurance lists as well as the debarment list. FDA did not concur with this plan, and stated that it is not in compliance

- with CFR 21 Subpart D 312.50-312.70—Responsibilities of Sponsors and Investigators.
- The above issue raised that of Investigators' qualifications. Pharmion stated that copies of Form 1572 and CVs of the Principal Investigators who conducted the CALGB studies were originally submitted to the NCI, and proposed to provide a letter of cross-reference to NCI's IND to access available investigator information. The FDA responded that this would be a review issue.
 - Regarding financial disclosure, Pharmion intends to request appropriate information from NCI and expects to certify on FDA Form 3454 either that there are no financial arrangements to disclose (box 2), or that we have been unable to obtain the information from the IND sponsor (box 3). The one exception is the fee paid to Dr. Lewis Silverman, the Principal Investigator of CALGB 9221, in consultation fees during data re-collection efforts. FDA concurred that the plan will meet FDA's financial disclosure requirement regarding the CALGB studies.
 - Questions regarding electronic NDA submission format, SAS datasets, laboratory dataset files, and CRFs (especially for the responders and subjects who developed AML by local site assessment, CALGB assessment, _____ assessment, and _____ assessment) were answered.
 - FDA reminded the sponsor that gender, race, and age analyses are required for both safety and efficacy. Office of Drug Safety advised on a proposal to reduce risks. The proposed name "Vidaza" was found acceptable. In addition, the sponsor was requested to make a presentation on each technical aspect of the NDA shortly before the NDA filing date, was reminded of the Financial Disclosure Final Rule, the Pediatric Final Rule, Pediatric Exclusivity provisions, information related to demographics, and presented with a list of Action Items.
5. On April 22, 2003 Pharmion submitted a Special Protocol Assessment Request (SN-024). In the proposed confirmatory trial only patients with MDS subtypes RAEB and RAEB-T will be enrolled. FDA made a number of comments on the protocol in a teleconference on July 22, 2003.
 6. At an internal meeting following-up on questions from the pre-NDA meeting and Special Protocol Assessment, FDA responses on "due diligence" in completing the confirmatory trial and adequacy of CALGB study data for filing the NDA reflect a reconsideration of the former position, in that the CALGB study data were thought to be sufficient for either full or accelerated approval, depending on detailed review of the data.
 7. A revised protocol of the confirmatory trial was submitted by the sponsor on August 20, 2003. In addition, the sponsor informed FDA that, while initially the sponsor encountered difficulties in re-collecting Study 9221 data from CALGB study sites, based on monitoring 22% of the sites, many of those issues were

resolved now that 100% of the data have been collected and analyzed for all 191 subjects at 53 sites who were randomized into this study. Pharmion had contracted _____ to collect data and monitor data collection activities. The data collected for Pharmion were source-verified, data-entered, and analyzed using a new electronic database. Data management and analysis were provided by _____ was provided for quality control of the final report by (_____ As a result,

- 190/191 (99.5%) subjects have baseline local pathology assessments.
- 188/191 (98%) subjects have CALGB central review assessments of diagnosis at study entry.
- 95% concordance for the diagnosis of MDS vs. non-MDS (in 173 out of 183 cases) was found between CALGB central pathologist and local hematopathologist at the time of diagnosis.
- 96%-99% of subjects in both treatment groups have key hematological (Hgb, WBC, and platelets) laboratory reports available.
- 80% (79/99) of azacitidine-arm subjects and 84% (77/92) of observation-arm subjects have reports of post-baseline bone marrow blast counts.

Many of the original investigators were no longer affiliated with the clinical sites at the time of data re-collection. In such cases, retrospective data re-collections were facilitated by the current Principal Investigator/Medical Reviewer at the clinical site. As part of the data re-collection, all available slides of bone marrow aspirates and biopsies and peripheral blood smears underwent an independent, blinded review by _____

The central CALGB review and a subsequent review by a consultant, _____ were quality assurance procedures, and were never intended to determine eligibility for enrollment or response. On the basis of located slides and readings, the concordance between _____ readings and the CALGB central reviewer readings was 88% (73/88); the concordance between _____ readings and those of local hematopathologist was 83% (73/88) for the diagnosis of MDS. Only 3 slides were available from the time of best response.

The results, as analyzed by Pharmion, confirm the conclusions of CALGB. There were 6 patients with CR and 10 with PR in the azacitidine group (before crossover of observation group patients) and none in the observation group (before crossover) for an overall response of 16.2%.

Reviewer's Note:

- *The concordance on MDS subtypes between site hemopathologists and central CALGB hemopathologist is less than the concordance on MDS vs. non-MDS as described above. The agreement between site pathology*

diagnosis and central CALGB pathology diagnosis of MDS subtypes (assuming that "low-risk subtypes" RA and RARS are equivalent, and "high-risk subtypes" RAEB and RAEB-T are equivalent) was 75.8% (75/99) in the azacitidine treatment arm, 73.9% (68/92) in the observation only arm, and 74.9% (143/191) for the entire ITT population.

- *If the assumptions are that the "low risk subtypes" RA and RARS are equivalent and the "high risk subtypes" RAEB and RAEB-T and also AML are equivalent (they differ only in the percentages of blast counts, an error-prone procedure), then the agreement between site pathology diagnosis and central pathology diagnosis was 78.8% (78/99) in the azacitidine treatment arm, 79.3% (73/92) in the observation only arm, and 79.1% (151/191) for the entire ITT population.*
- *The chief hematopathologist at NCI, Dr. Elaine Jaffe, considers a 67% inter-pathologist agreement to be typical for MDS subtypes (personal communication).*

E. Important Issues with Pharmacologically Related Agents

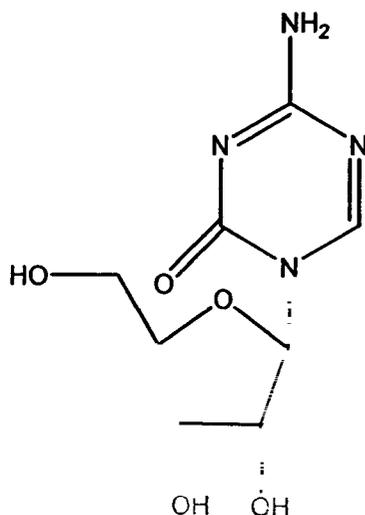
Azacitidine is an inhibitor of uridine kinase and of DNA methyltransferase. Demethylation of DNA is thought to be the main pharmacodynamic action of the drug. The only other pharmacologically related agent is decitabine (5-aza-2'-deoxycytidine; NSC-127716). Chemically unrelated hydroxyurea is also a DNA methyltransferase inhibitor.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Clinically relevant findings include the following:

- Azacitidine (5-azacytidine) is an analog of the naturally occurring pyrimidine nucleoside cytidine. It differs from cytidine by having nitrogen in the 5 position of the heterocyclic ring.

**APPEARS THIS WAY
ON ORIGINAL**



Its synthesis was reported in 1964 by scientists in the Czech Academy of Sciences; it received a U.S. patent in 1965 and 1967 (The Merck Index, 12th ed).

- In aqueous solutions azacitidine undergoes spontaneous hydrolysis to n-formylguanylrribosylurea and to guanylrribosylurea. For this reason azacitidine should be used within 1 hour if kept at room temperature and within 8 hours if kept at between 2°C and 8°C.
- Animal toxicology studies have been carried out in mice, rats, dogs, and Rhesus monkeys. Bone marrow, liver, kidney, and lymphoid tissues have been identified as target organs of toxicity. Most of these studies were performed during 1970s and early 1980s. The lethal dose of azacitidine after IV administration in mice, rats, and dogs was approximately 250 mg/m². Repeated daily dosing appears to increase the toxicity of azacitidine.
- Azacitidine is genotoxic *in vitro* and carcinogenic in many animal species, indicating a potential risk of secondary cancers in humans.
- Teratogenic and spermatotoxic effects in rodents suggest caution in the use of azacitidine in pregnant women or women of child-bearing potential, as well as in men whose sexual partners are women of child-bearing potential.

III. Human Pharmacokinetics and Pharmacodynamics

According to the results of the AZA-2002-CSR-004 study submitted by the sponsor and published information,

- C_{max} was observed after 11 minutes following a 10-minute IV infusion of 75 mg/m² azacitidine, and after 30 minutes following SC administration of the same dose.
- The mean maximum azacitidine plasma concentration following IV administration was approximately 4-fold higher than that following SC administration. The geometric mean peak plasma azacitidine concentration following SC administration was approximately 3 μM.

- The mean plasma half-life following IV administration was approximately 22±1 min and following SC administration was approximately 41±8 min.
- The mean volume of distribution after IV administration was 76 L, which is greater than the total body water volume (42 L) suggesting extensive tissue distribution.
- The mean plasma AUC after SC administration was about 90% that of IV administration. The variability of individual ranged from about 60% to 128% of the mean. The absolute bioavailability of 89% was calculated by the ratio of AUC SC geometric mean to AUC IV geometric mean with a 90% confidence interval of 70% to 112%.
- Azacitidine metabolism in humans has not been evaluated. *In vitro* studies conducted with human hepatic S9 fractions indicate that azacitidine may undergo hepatic metabolism.
- Urinary excretion is the primary route of azacitidine elimination after IV administration (85% vs. <1% fecal elimination). The mean excretion of radioactivity following radiolabeled azacitidine SC administration is 50%. The mean elimination half-life of total radioactivity following IV administration of radiolabeled azacitidine is 3.5 hours, and following SC administration, 4.5 hours.
- The MTD IV dose of azacitidine has been reported to be 150 to 200 mg/m²/day when given daily for 5 days every 14 to 21 days. The MTD IV dose was reported to be about 500 mg/m² when administered weekly, and 150 mg/m² when given twice weekly.
- The MTD of azacitidine administered SC has not been determined. Doses up to 150 mg/m²/day were administered to some patients in the CALGB MDS trials reviewed in this NDS (See Safety section).
- Interactions of azacitidine with other drugs have not been tested.
- There is insufficient information on whether azacitidine is a substrate of cytochrome P450 enzymes. The sponsor conducted *in vitro* studies with human liver microsomes to investigate whether azacitidine inhibits CYP 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4, but the results are inconclusive. Azacitidine is not an inducer of CYP 1A2, 2C19 or 3A4/5, as tested in human hepatocytes.
- There are no pharmacodynamic parameters to be followed, except myelotoxicity.

IV. Description of Clinical Data and Sources

A. Overall Data

NDA 50-794 N-000 was submitted electronically. The primary efficacy and safety data are data from three clinical studies conducted by Cancer and Leukemia Group B (CALGB). CALGB Study 9221 is the Phase 3 pivotal study that was designed to provide primary evidence for efficacy of azacitidine in the treatment of MDS. CALGB 8421 and CALGB 8921 studies provide additional support for efficacy and provide additional safety data. The results of all three studies have been published.

B. Tables Listing the Clinical Trials

Study number	Design	Dosage Regimen	# of patients	MDS Subtype
CALGB 9221	Phase 3, 2-arm, controlled, open label, multicenter (cross-over allowed)	Azacitidine 75 mg/m ² SC x 7 days in 28-day cycles vs. best supportive care	191 (99 in azacitidine arm; 92 in BSC arm)	RA, RARS, RAEB, RAEB-T, CMMoL
CALGB 8921	Phase 2, single arm, multicenter, Open label	Azacitidine 75 mg/m ² SC x 7 days in 28-day cycles	72	RAEB, RAEB-T, CMMoL
CALGB 8421	Phase 2, single arm, multicenter, open-label	Azacitidine 75 mg/m ² IV x 7 days in 28-day cycles	48	RAEB, RAEB-T

C. Postmarketing Experience

N/A.

D. Literature Review

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V. Clinical Review Methods

A. How the Review Was Conducted

The review followed this sequence:

- A survey of current literature on diagnosis, classification and treatment of MDS, using standard textbooks, reviews, and publications listed in PubMed
- Review of the current recommendations of an international working group to standardize 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
- Review of supporting tables for various aspects of the trial and evaluation of Sponsor's claims
- Review of patient narratives and of e-CRFs in selected cases
- Consultations with Pharmacology and Statistics reviewers
- Requests for additional information from the Sponsor
- Formulation of conclusions and recommendations, and
- Evaluation of proposed labeling changes, and revision of these changes.

B. Overview of Materials Consulted in Review

References to cited literature, to Efficacy and Safety reviews of the original NDA, and to reviews by other reviewing disciplines are described in the text.

The entire NDA supplement was submitted electronically. The data sets were examined for all aspects of the trial, including patient disposition, efficacy and safety.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The NDA was checked for internal consistency of reported results, consistency of results in the NDA and of published reports of the trials. Reports of all the responders were examined in detail. Great care was taken with accounting of the disposition of all the subjects enrolled in the trial.

The Division decided against a Division of Scientific Investigation (DSI) audit for several reasons.

- As described above in Section I.D. Other Relevant Information, the three clinical trials were not conducted by a sponsor, i.e. a pharmaceutical company, but by Cancer and Leukemia Group B (CALGB) under the auspices of NCI. While the trial was ongoing, CALGB conducted audits of individual sites. The CALGB regulatory records of the trials were destroyed as per CALGB policy 3 years after completion of the trial. The sponsor obtained access to the original documentation at the study sites and was successful in re-creating all the

datasets (as described above in Section I.D.). The Division felt that the study records were examined both at each study site and in the central CALGB office and that there was no motive and little opportunity for falsification of data. In addition, the results were subsequently published in medical literature. The results as submitted by the sponsor and as published are consistent.

- CALGB investigators had no financial gain in falsifying data, while they had great interest in satisfying CALGB and NCI criteria for good clinical data management in order to continue participating in CALGB trials.
- The response rates in the two largest sites were not different from response rates in other sites.
- There was consistency in response rates among sites. There was no one site that was driving the response data.
- Similar response rates in MDS were reported in other clinical studies, described above.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials in this NDA were conducted in accordance with CALGB standard operating procedures for clinical investigations, which ensured compliance with Office of Human Research Protections (OHRP), DHHS, and FDA Good Clinical Practice (GCP) regulations governing research in human subjects. These studies were initiated prior to implementation of International Conference on Harmonization (ICH) GCP Guidelines.

- 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, 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.
- Additional subject consent was not required for data re-collection by the sponsor; the original consent form was adequate.

E. Evaluation of Financial Disclosure

Since NCI is a public institution, Pharmion requested appropriate information from NCI regarding financial disclosure. Pharmion submitted FDA Form 3454 indicating it has acted with due diligence to obtain the information required under 21 CFR 54.4 and been unable to obtain the information from the IND sponsor (box 3). The reason why this information could not be obtained is attached.

1. Attachment to Form FDA 3454 Certification: Financial Interests and Arrangements of Clinical Investigators

The National Cancer Institute (NCI) was the Part 54 sponsor of the studies submitted in support of this application.

Pharmion acted with due diligence and requested that NCI provide information required under 21 CFR 54.4 for financial interests and arrangements of clinical investigators. NCI indicated that CALGB studies 8421, 8921, and 9221 were conducted prior to the implementation of their program to collect financial disclosure forms in compliance with 21 CFR 54.4. Thus, they could not provide this information for these studies. NCI currently collects financial disclosure forms annually with all NCI-registered investigators in compliance with 21 CFR 54.4. NCI has provided a cross reference to their DMF which provides details of how investigator registration is currently handled.

Since the Part 54 sponsor was a public institution:

It is unlikely that compensation provided by NCI to investigators was affected by the outcome of the studies.

It is unlikely that NCI provided significant payments of other sorts.

It is not possible for any investigator to hold a significant equity interest in the sponsor of the study.

In addition, since Pharmion owns all rights to azacitidine for the treatment of MDS, we know that no investigator holds a proprietary interest in the tested product.

The sponsor also attached one form FDA 3455 for Dr. Lewis R. Silverman, the Principal Investigator of CALGB 9221, in consultation fees during data re-collection efforts. These fees were disclosed as "...any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;.." The attachment to Form FDA 3455 describes the circumstances of these payments.

2. Attachment to Form FDA 3455 Disclosure: Financial Interests and Arrangements of Clinical Investigators

The CALGB cooperative group Studies 8421, 8921, and 9221 using azacitidine in the treatment of subjects with myelodysplastic syndrome were conducted under the sponsorship of NCI (IND #7574) and the FDA under an orphan drug grant. These studies were conducted in 1985-1997 prior to the implementation of Financial Disclosure of Clinical Investigators as defined in 21 CFR 54. According to FDA's March 20, 2001, guideline on financial disclosure, "The IND/IDE sponsor is responsible for ensuring that required financial information is collected and made available to the applicant company, so that the information can be included in the NDA/BLA/PMA submissions." Because NCI is a public institution that is not a commercial entity, an investigator would be unable to hold an equity interest, and there are unlikely to be any other financial arrangements to disclose. Pharmion was incorporated as a company on January 2000 and, thus, did not have any vested interest with CALGB or its investigators during the prospective conduct of these studies.

However, although the studies were conducted by NCI, Pharmion undertook the data recollection efforts for these CALGB studies in 2002 after acquiring marketing rights in July 2001 from Pharmacia and data rights from NCI in November 2001. Pharmion has not paid any investigator in connection with the conduct of this study apart from Lewis R. Silverman, M.D., the lead investigator for CALGB Study 9221. Dr. Silverman has a consulting agreement with Pharmion Corporation to provide unique information, experience and skill related to the clinical development of azacitidine. This consulting agreement was implemented 01 December 2001 and includes

— by Dr. Silverman in the performance of these services, including
 — Pharmion has paid Dr. Silverman a total of — in consulting fees since the implementation of this consulting agreement.

Pharmion independently collected and analyzed data from these CALGB studies to minimize potential bias of clinical study results by the disclosed arrangement of interest.

During the Pre-NDA meetings, FDA concurred that the sponsor's plan will meet FDA's financial disclosure requirement regarding the CALGB studies.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

- Treatment with azacitidine SC or IV is effective in about 15% of patients with all types of MDS subtypes in inducing prolonged responses, with complete or partial normalization of peripheral blood counts and bone marrow blast percentages and with decreased or absent transfusion requirements. There

were 0% responses among observation only MDS subjects. The difference between response rates in the azacitidine-treated subjects and in the observation alone subjects in the randomized trial was statistically significant ($p > 0.0001$).

- The results of the 3 CALGB trials in which 238 MDS subjects were treated with azacitidine are consistent, with response rates ranging from 12.7% to 19.1%. Response rates were similar in all 5 MDS subtypes. Response rate to azacitidine treatment in 28 subjects diagnosed with MDS at treatment sites and adjudicated to have AML by the CALGB central laboratory was about 18%.
- The pivotal trial was a randomized, controlled trial consisting of an azacitidine arm (99 subjects) and an observation arm (92 subjects). However, subjects in the observation arm were permitted to cross over to the azacitidine arm, if they met pre-specified criteria of transfusion dependence, thrombocytopenia or neutropenia. Over one-half (51) of the subjects in the observation arm crossed over to azacitidine treatment. The remaining observation only subjects (36) no longer matched the azacitidine treatment subjects with respect to MDS subtypes and therefore could not serve as comparison group to the azacitidine treatment group in various secondary efficacy parameters.
- The responses were long lasting in most patients. The duration of responses cannot be accurately estimated, because at the time of withdrawal from trials over 70% of subjects remained in response status.
- In addition to complete or partial responses azacitidine treatment resulted in lesser responses, termed Improvement, which occurred in about 16% of patients in the 3 trials, consisted of increased blood counts and loss of transfusion dependence, and lasted for a median duration of 195 days. Improvement occurred in about 5% of patients in the observation only arm, but was it lasted a short time and was of little benefit.
- In the controlled trial, there was no statistically significant difference in survival or in progression to AML, if the azacitidine treatment group was compared to the observation group that included both subjects who crossed over to azacitidine treatment and those who did not. In exploratory sub-set analysis, subjects treated with azacitidine had longer survival and delayed progression to AML as compared to observation only subjects; however, these groups were no longer matched by MDS subtype as noted above.
- Follow-ups in all three CALGB trials were as long as 8 years after subject withdrawal, and the percentage of subjects followed up was between 80% and 90%.

B. General Approach to Review of the Efficacy of the Drug

This NDA contains the results of one controlled trial (azacitidine vs. observation) and two single-arm uncontrolled trials in support of the proposed indication. The clinical trials are reviewed below.

C. Detailed Review of Trials by Indication

1.1 Title of the Pivotal Study: CALGB Study 9221. A Randomized Phase III Controlled Trial of Subcutaneous 5-Azacitidine (NSC # 102816) vs. Observation in Myelodysplastic Syndromes.

1.2 Study Period: February 7, 1994 (first subject signed the Informed Consent) to October 30, 2002 (last subject had the last follow-up).

1.3 Investigators and Study Centers: There were 102 investigators at 53 sites, all in U.S.

1.4 Study Objectives: As reformulated by the sponsor, the primary objective was to determine the overall response rate (CR + PR) to azacitidine in comparison to an untreated observation group. The secondary endpoints used in the statistical analyses of this NDA are stated in the Statistical Section. The CALGB Study 9221 protocol specified both the primary endpoint and the following secondary endpoints: to determine the impact of azacitidine on red cell transfusion requirements, platelet counts, absolute neutrophil counts (ANC), rates of infection and hemorrhage, and percent bone marrow blasts in comparison to an untreated observation group.

1.5 Overall Study Design: This was a Phase 3 multicenter, U.S. academic medical center, randomized, open-label, controlled study designed to compare azacitidine plus supportive care with an observation group receiving best supportive care in subjects with any of the five subtypes of MDS (RA, RARS, RAEB, RAEB-T, and CMMoL).

The study was designed to allow subjects randomized to the observation group to cross over to azacitidine treatment after meeting protocol criteria, which were increases in marrow blasts, decreases in Hgb or platelets, increased RBC or platelet transfusion requirements, and clinical infection with low ANC and requiring antibiotics.

1.6 Study Plan:

1.6.1 Assessments:

- Baseline studies: history & physical, CBC, platelet count, reticulocyte count, bone marrow aspirate & biopsy, cytochemical studies, serum Fe and B₁₂, RBC folate, LAP, chemistries, ECG, Chest X-ray, UA.
- Studies before each 28-day cycle: Physical, CBC, platelet count, reticulocyte count, blood chemistries, adverse events.

- Studies in azacitidine group only: CBC, platelet count, reticulocyte count, bone marrow biopsy & aspirate once during nadir, Day 57, Day 113 and every 2-3 months.
- Studies in observation group only: CBC, platelet count, reticulocyte count every 2 weeks for 16 weeks, then monthly; Bone marrow aspirate & biopsy on Day 57, Day 113 and every 3-4 months.
- At Onset of CR: physical examination, CBC, platelet count, reticulocyte count, bone marrow aspirate & biopsy, cytochemical studies, Fe content, LAP.
- During Stable Remission on Treatment (PR or Improved after 4 cycles): bone marrow aspirate & biopsy every 3-5 months.
- Post-treatment (until death or second malignancy): physical examination, CBC, platelet count monthly for 6 months, then every 2 months.
- Quality of life measures: at baseline, during Weeks 7, 15 and 26.

1.6.2 Selection of Study Population:

Inclusion Criteria:

- RA and RARS subjects were included, if they met one or more of the following criteria:
 - Required RBC transfusions for ≥ 3 months for symptomatic anemia
 - Had platelet counts $\leq 50 \times 10^9/L$, or significant clinical hemorrhage
 - Required platelet transfusions, or
 - Were neutropenic ($ANC < 1 \times 10^9/L$) with infections requiring treatment with antibiotics.
- Age > 15 years
- Life expectancy ≥ 2 months
- Performance status 0-2
- Bone marrow aspirate/biopsy with differential count of ≥ 200 cells
- Total bilirubin $\leq 1.5 \times ULN$; ALT/AST $\leq 2 \times ULN$; serum creatinine $\leq 1.5 \times ULN$; serum $CO_2 \geq 19$ mEq/L
- Had not received radiation or chemotherapy for cancer within 6 months, and free of malignancy for the previous 3 years
- Signed Informed Consent

Exclusion criteria:

- Pregnancy
- Medical or psychiatric illness that limited survival to < 6 months
- Uncontrolled CHF
- $> 30\%$ myeloblasts in the bone marrow or M6 leukemia (FAB criteria)
- Prior cytotoxic therapy for MDS
- Treatment with corticosteroids, interferon, or retinoids within 1 month before study entry
- Prior treatment with filgrastim, sargramostim, IL-3 or other hematopoietic growth factors. Prior use of erythropoietin acceptable.

- Prior treatment with azacitidine
- Previous history of leukemia

Removal of Subjects from Therapy or Assessment

- Subjects with CR after 3 more cycles of therapy
- Failure to demonstrate CR, PR, or Improvement after 16 weeks of azacitidine treatment.
- Relapse (to be followed only for survival and second malignancy)
- Treatment failure, i.e. diagnosis of AML (to be followed only for survival and second malignancy)
- Subject's refusal to continue protocol therapy or protocol detrimental to the condition of subject (to be followed for survival and second malignancy, except that collection of data forms and flow sheets were to be continued in subjects with CR, PR or Improvement)

1.6.3 **Randomization:** Registration was controlled by the CALGB Registrar. Blocked randomization, stratified by the 5 MDS subtypes, was used to assign subjects to the treatment and observation arms. The five subtypes of MDS were to be balanced between study arms.

Blinding: This was an open label study.

Azacitidine Dose and Method of Administration: Subjects in the azacitidine treatment arm were to receive 75 mg/m² azacitidine SC daily for 7 days every 28-day treatment cycle for a minimum of 4 cycles. Actual body weight and height were to be used to calculate body surface area to determine dosage before each treatment cycle. The dose could be adjusted (increased, decreased, or delayed) at the beginning of any cycle, based on predefined hematologic and renal laboratory results.

Dosing information, including BSA, total dose (mg/m² and mg) per daily dose, and number of days the drug was administered each cycle were to be recorded on the CALGB Drug/Blood Sheet and the CALGB Flow Sheet.

Subjects were provided with "Instructions for Patients on the Preparation and Administration of Subcutaneous 5-Azacitidine" and either self-administered the drug or had a caregiver administer it.

After 4 cycles, patients with CR were to receive 3 more cycles; patients with PR or Improved were to continue until CR or Relapse; and patients with no response were to be taken off the study.

1.6.3 **Dose adjustments** based on hematological toxicity and on renal dysfunction, as detected by serum CO₂, BUN or creatinine, are specified. Criteria for dosage adjustments were pre-specified. Dose adjustments were based on hematological toxicity (WBC >3,000/μL, ANC >1500/μL and platelets

>75,000/ μ L) and renal function abnormalities (CO_2 >19 mEq/L, BUN or creatinine >2x baseline). If no beneficial effect occurred after the first 2 courses and no toxicity had occurred, the dose was to be escalated to 100 mg/m²/day for Cycle 3, and to 150 mg/m²/day for Cycle 4.

1.6.4 Concomitant Therapy: Prohibited are hematopoietic growth factors. Allowed are blood transfusion products, oral antibiotics, antiemetics, analgesics and antipyretics, IV replacement solutions.

1.6.7 Efficacy Variables: Overall response rate (CR + PR) was defined as the primary efficacy endpoint. Changes in RBC and platelet transfusions, in Hgb concentrations, WBC, ANC and platelet counts, in rates of infections requiring antibiotic therapy, in rates of hemorrhage, and in percent of marrow blasts were secondary efficacy endpoints. (CALGB protocol for this trial specified all of the above as primary efficacy variables).

1.6.8 Criteria for Response: The criteria used for the overall response assessment were similar to response criteria for AML, because there were no previous response criteria for MDS. These criteria were similar to MDS response criteria published by the International Working Group (IWG). The Response Criteria for all types of MDS are shown in the Reviewer's Table below.

Response Type	Criteria for Response
Complete (CR)	Normal CBC and absence of myeloblasts in peripheral blood and <5% myeloblasts in the bone marrow for at least 4 weeks.
Partial (PR)	<u>Peripheral blood criteria</u> : $\geq 50\%$ restoration in the deficit from normal levels of baseline Hgb, WBC, and platelets, and no myeloblasts. For CMMoL, if WBC is elevated at baseline, a 75% reduction in the excess count above ULN. <u>Marrow criterion</u> : for RAEB, RAEB-T & CMMoL, $\geq 50\%$ decrease in myeloblasts from baseline. For RA & RARS, marrow criterion N/A. Duration of the above responses for at least 4 weeks.
Improvement	$\geq 50\%$ restoration in the deficit from normal in one or more peripheral blood cell lines, but insufficient to meet criteria for PR, or a $\geq 50\%$ decrease in RBC or platelet transfusion requirements. <u>Note</u> : improvement constituted a remission for the purpose of follow-up.

1.6.9 Criteria for Relapse

- In subjects with CR: increase of blasts in marrow to >5%
- In subjects with PR: >30% blasts in marrow

1.6.10 Criteria for Disease Progression: These criteria had to be met in order for those subjects randomized to the observation arm to be eligible for

crossover to the azacitidine arm (shown in Reviewer's Table below, from pp. 46, Final Study Report, CALGB 9221)

MDS Type	Criteria for Disease Progression
RA, RARS, or CMMoL	Increase in marrow blasts to $\geq 15\%$ on 2 aspirates at least 1 week apart. Crossover from observation group could occur after Day 56.
RAEB	Increase in marrow blasts to $>25\%$ on 2 aspirates performed at least 1 week apart, resulting in RAEB-T. Crossover from observation group could occur after Day 56.
RAEB-T	An increase in marrow blasts to $>30\%$ but $<40\%$. Crossover from observation group was to be immediate. An increase in blasts $>40\%$ was reason for removal from study.

1.6.11 Criteria for Stable Disease: Subjects who had a valid assessment for response, but did not meet the criteria for CR, PR, Improvement, or Progression, were considered stable.

1.6.12 Criteria for Crossover (RBC, ANC, and Platelet Criteria): shown in Reviewer's Table below (from pp. 46-7, Final Study Report, CALGB 9221)

Blood Cell Type	Blood Cell Criteria for Crossover from Observation to Azacitidine Group
RBC	On Day 113, if transfusion-dependent at entry or onset of transfusion requirement while in observation group; if Hgb decreased to ≤ 8.0 g/L (<65 years old) or ≤ 9.0 g/L (≥ 65 years old); if transfusion required for other documented reason, except surgery.
Platelet	On Day 57, if platelet count $<20,000/\mu\text{L}$ or platelet transfusion required; if platelet transfusion was required for major hemorrhage regardless of platelet count.
Neutrophil (ANC)	On Day 57, if ANC was $<500/\mu\text{L}$ and clinical infection with fever $\geq 101^\circ$; or crossover after the infection was under control.
Trilineage	If in Weeks 15 and 16 or any 2 successive weeks thereafter, Hgb + ANC + platelets decreased by $>25\%$ compared to entry values; 2 of 3 decreased by $\geq 50\%$, or 1 of 3 decreased by $\geq 75\%$ compared to entry values.

1.6.13 Data Quality Assurance:

- CALGB 9221 Study was monitored for safety and efficacy according to prevailing CALGB policies and procedures that ensured compliance with OHRP, NIH, and FDA regulations governing research in human subjects. About 26% of the subjects' records collected during the prospective conduct of this trial were independently audited by the CALGB Data Audit Committee (audit certificate is included in the NDA).
- Retrospective Data Collection and Analysis Plan. The sponsor developed a Retrospective Data Collection and Review Plan for collecting retrospective study data, since a large proportion of the

CALGB data were no longer available. The following steps were taken to ensure that re-collected data were accurate and reliable:

- All data were to be collected on CRFs prepared individually for each subject. Data were transcribed by a — study coordinator and was verified against original documentation by a — clinical research associate.
- The primary source for retrospectively collected data was the subjects' original hospital or clinic medical records. Research records or CALGB Flow Sheets and Forms were used when primary source records were not available.
- Many of the original investigators who participated in the CALGB 9221 study were no longer affiliated with the clinical sites at the time of data re-collection. In such cases, the current Principal Investigator or — clinical research associate (study monitor) made the adjudications on the relationship of AEs to study medication, determined the degree of toxicity, or assigned clinical significance.
- — conducted independent good clinical practice (GCP) audit.
- A comprehensive end-study audit of data was performed on a subset of randomly selected subjects. During the audit, the electronic data was manually compared to the CRF data to determine the data entry error rate. The initial audit of 14 subjects' 284,495 data fields had an error rate of 0.007%; therefore, no additional subject data were reviewed.

As a result of implementation of this plan, the following statistics highlight the amount of source-verified data available to support the diagnosis of MDS and to determine the response rates for the entire subject population:

- Diagnosis of MDS data: Reports of the baseline bone marrow assessments by the local hematopathologist were retrieved for 190/191 (99.5%) subjects. Central CALGB pathology reviewer reports were retrieved for 188/191 (98%) subjects. The central reviewer was able to evaluate 183/188 (97%) slide sets. Concordance between the local hematopathologist and the central reviewer on the diagnosis of MDS was 95% (173/183 slide sets). The review at central CALGB, which was carried out in batch analysis, was intended to provide a level of quality assurance of the accuracy of diagnosis and response. It was never intended to determine the eligibility of enrollment or the response. For this submission the sponsor asked — to carry out an independent review of all available slides. Baseline slides were located for 97/191 (51%) subjects, of these 88 were still of adequate quality for review. The concordance between — review and that of the central CALGB reviewer (88%; 76/86) and the local pathology review (83%; 73/88) for the diagnosis of MDS was similar.

Only 3 subjects had slides from the time of best response; all 3 hematopathologists agreed with their interpretations. If any of the three hematopathologists diagnosed AML instead of MDS, the patient was classified as having AML.

- Peripheral blood and marrow response data: Data on Hgb, WBC and platelet counts were located in $\geq 96\%$ of subjects. Marrow blast values (baseline and at least one post-baseline) were available for 89% and 80% of subjects, respectively, in the azacitidine arm; and for 88% and 84% of subjects, respectively, in the observation arm.
- Transfusion response data: RBC and platelet transfusion data during the study were located for 100% of subjects in both arms of the study. RBC and platelet transfusion data for 3 months prior to study entry was not required by the CALGB protocol except for RA and RARS subjects; the retrospective attempt to collect transfusion information prior to study entry “yielded limited results.”
- Infection response data: Antibiotic usage data, as a surrogate for infection, were located for 96/99 (97%) azacitidine subjects at baseline and 99/99 (100%) post-baseline; and for 86/92 (94%) observation subjects at baseline and 92/92 (100%) post-baseline.
- Hemorrhage response data: Source-verified hemorrhage data were located for 96/99 (97%) azacitidine subjects at baseline and for 100% of subjects post-baseline, and for 86/92 (94%) observation subjects at baseline and 100% post-baseline.
- Dosing information: BSA, total dose per injection and number of days drug was administered each cycle was recorded on the CALGB Drug/Blood Sheet, which provided data for 100% (99/99) of azacitidine subjects. At least one weight value and one height value is available for 98/99 (99%) azacitidine subjects.

1.6.14 Statistical Methods

- The sponsor developed a Statistical Analysis Plan specifically for the data management and analysis of the retrospectively collected data. The original CALGB Statistical Analysis Plan is attached to the application.
- Efficacy: ITT population, consisting of all subjects randomized in the study, was to be used for analyses of efficacy data. Testing of interactions was to be conducted at the $\alpha=0.10$ level. All other testing was to be conducted at the 2-sided $\alpha=0.05$ level with 95% CIs.

- **Primary efficacy.** The protocol defined response as CR, PR or Improvement. For the purposes of these retrospective analyses, the primary endpoint was defined as CR or PR, with the best response attained during the study used to characterize each subject. A secondary analysis was CR rate alone. Separate response rates were to be computed for CR, PR, and overall response (CR + PR). The response rates were also to be presented for each MDS subtype and for AML.
- Analysis of response rate in the azacitidine group compared to the observation group was to be provided. The comparison of the rate of CR + PR was to be the primary analysis. Response rates from the two groups were to be compared using a multivariate logistic regression model, adjusting for the baseline MDS diagnosis. Fisher's Exact Test was used to compare groups.
- **Secondary efficacy.** The secondary efficacy objectives were red cell and platelet transfusion requirements; Hgb, WBC, platelet count, and absolute neutrophil counts (ANC) counts; rates of infection and of hemorrhages; percent bone marrow blasts in comparison to an untreated observation group, and time-to-event summaries of death, disease progression, relapse, transformation to AML, and time to transformation to AML or death. All secondary efficacy summaries were to be descriptive, presenting frequencies or means, and no inferential testing was to be presented. Changes in the rates of transfusions, antibiotic courses, and hemorrhages were analyzed by Wilcoxon Rank Sum test. Time-to-event summaries (death, disease progression, relapse, and transformation to AML, and time to transformation to AML or death) were to be summarized using Kaplan-Meier methods.
- **Safety.** Safety data were to be collected from the time of informed consent through 30 days after the last dose of study medication in the ITT population. Standard definitions of adverse events, treatment-emergent adverse events, SAEs are provided.
- **Clinical laboratory evaluations.** Numeric laboratory results were to be summarized with descriptive statistics, and categorized as missing, low, high or within normal range. CALGB used CTC toxicity grade, ranging from 0 to 4.
- **Other safety evaluations.** Physical examinations, vital signs, chest X-rays, ECGs and other such data will be descriptively summarized by study group.
- **Sample size determination.** The sample size for CALGB 9221 study was based on response rate, defined as subjects achieving CR, PR, or Improvement. The study was designed to have adequate power to

detect a difference in response rate between treatment arms of 20% (10% vs. 30%). A maximum of 158 subjects (79 per arm) was required for 88% probability of rejecting the null hypothesis. A 10% overage, or 174, was calculated to allow for potential dropouts or non-evaluable subjects. For this study report (the submitted NDA), analysis of response rates was based on CR or PR, resulting in lower expected response rates than originally projected in the CALGB Protocol 9221. The lower response rates together with the larger actual sample size of 191 would increase the power of the study to detect a 20% difference.

- Changes in the conduct of the study or planned analyses. Four protocol amendments were generated during the conduct of the study. None affected the statistical analysis plan. However, prior to Amendment 3, which excluded subjects with prior history of leukemia, one subject with prior history of leukemia had entered the study.
- Changes to planned analyses. The following are the key changes in the statistical analysis plan from the original CALGB 9221 protocol:
 - Primary efficacy endpoint: response rate based on peripheral blood and bone marrow findings. Response was defined as CR + PR, instead of CR + PR + Improvement.
 - Secondary endpoints: RBC and platelet transfusions; Hgb, WBC, ANC, and platelet counts; courses of antibiotic therapy; hemorrhage rates, and % marrow blasts. These endpoints were not changed.
 - Identifying 5 categories of major protocol violations that would be used for subset analyses for efficacy.
 - Analyses of survival with and without the subjects who had an adjudicated diagnosis of AML at baseline.
 - Excluding analyses of QOL data, and interim analyses.
 - Duration of clinical response was calculated manually as the time that all values for blood and bone marrow blasts that were abnormal at baseline were repeatedly within the range that met at least PR criteria.

1.7 CALGB 9221 Study Results

- 1.7.1 Disposition of study subjects: A total of 191 subjects were enrolled in this study at 53 sites. The number of patients that were screened but not enrolled is not known.

- Of the 191 subjects enrolled, 99 were randomized to azacitidine arm and all received study medication
- 92 were randomized to the observation arm; 51/92 (55%) crossed over to the azacitidine arm and all received study medication. The remaining 41 subjects in the observation arm received only “best supportive care”. Overall, 150 subjects were treated with azacitidine.
- Four of the 53 study sites enrolled 10 or more subjects (10-24 subjects per site). These 4 sites enrolled 31% (59/191) of the total enrolled population. Most sites enrolled 5 subjects or fewer.
- Sponsor’s Table 10.1-1: Subject Disposition and Completion Status summarizes the disposition of all subjects during the course of the study and their status at follow-up. Completion status was available on 190 of the 191 enrolled subjects. The one remaining subject (#59418) was randomized to the Observation arm on May 25, 1995 and remained in the study at the time of last contact on 16 April 2002. This subject had stable disease, did not cross over to the azacitidine arm, and did not progress to AML.

**Reviewer’s Table on Reasons for Withdrawal from
Therapy/Observation¹ (ITT Population)**

Reasons for withdrawal	Azacitidine N=99 (%)	Azacitidine after Crossover N=51 (%)	Observation (No crossover) N=41 (%)
CR, therapy d/c’d	5 (5.1%)	3 (5.9%)	0
Completed Rx per protocol	1 (1%)	3 (5.9%)	0
Developed AML	14 (14.1%)	6 (11.8%)	18 (43.9%)
Relapse after CR, PR, or improvement	3 (3%)	0	N/A
No response after 4 cycles of Rx	17 (17.2%)	13 (25.5%)	N/A
Adverse event	8 (8.1%)	5 (9.8%)	1 (2.4%)
Death	11 (11.1%)	9 (17.7%)	6 (14.6%)
Subject withdrew from study	16 (16.2%)	9 (17.7%)	2 (4.9%)
Investigator discretion	11 (11.1%)	7 (13.7%)	1 (2.4%)
Other ²	21 (21.2%)	5 (9.8%)	12 (29.3%)

¹From Sponsor’s Table 10.1-1: Subject Disposition and Study Completion Status. More than one reason may apply.

²Listed in Appendix 16.2.9.13.2, including no reason given for 2 subjects (poor compliance for one in the Observation group, and one lost to follow-up).

- A common reason for withdrawal from both study arms was the development of AML, more common in the Observation Only group than in either of the azacitidine groups.
- Another common reason for withdrawal in the azacitidine groups was no response to 4 cycles of treatment.
- Death was about as common in all three groups.

- Withdrawals due to adverse events were much more common in the azacitidine groups than in the Observation group, as were withdrawals at the investigator's discretion, which were due either to drug toxicities (increased cytopenias) or to disease progression (increased blasts).

Follow-up status was ascertained as late as 2250 days (>6 years) after study withdrawal (range, 2 to 2250 days) or over 2700 days (>7 years) after entry into the study. In the Reviewer's Table below the numbers reflect the incidence after withdrawal from the study, with the exception of progression to AML, which includes the total incidence both on study and after the study.

Reviewer's Table on Follow-up Status After Study Completion¹ (ITT Population)

Follow-up status	Azacitidine N=99	Azacitidine after crossover N=51 (%)	Observation (No crossover) N=41 (%)
Follow-up contact made	87 (87.9%)	42 (82.4%)	35 (85.4%)
Subject died	84 (84.9%)	38 (74.5%)	33 (80.5%)
Progressed to AML ²	40 (40.4%)	17 (33.3%)	21 (51.2%)
Diagnosed with another malignancy	1 (1%)	3 (5.9%)	3 (7.3%)
Subsequent radiation therapy	3 (3%)	2 (2.9%)	1 (2.4%)
Subsequent chemotherapy	35 (35.4%)	23 (45.1%)	27 (65.9%)

¹Data from Sponsor's Table Table 10.1-1.

²Total incidence both on study and after withdrawal from study.

The percentages of patients who progressed to AML were slightly higher in the Observation group than in the azacitidine groups, but all are consistent with data published in the literature for high-risk MDS groups. The percentage of patients who received subsequent chemotherapy were higher in the Observation group than in the two azacitidine groups.

1.7.2 Major Protocol Violations:

Thirty-four patients randomized to the Azacitidine Group and 32 patients randomized to the Observation Group had taken hematopoietic growth factors at any time, or systemic steroids in the month before or during the study to treat TEAEs such as bone pain, rash, hives, and infections. Three patients in the azacitidine group and 2 patients in the Observation Group did not meet the eligibility criteria of an established diagnosis of MDS. In the azacitidine group, one patient had a prior history of leukemia; one patient had a site diagnosis of RAEB-T with 14.9% myeloblasts rather than 20%; and one patient had a diagnosis of RA on the basis of a bone marrow aspirate 2 weeks before entry, but the slides could not be located at a later time. In the Observation Group, 2 subjects had >30% blasts; one of the patients later crossed over to azacitidine treatment, the other remained in the Observation Group.