3.5 Study Plan: Assessments as described in CALGB 9221. Subjects were to receive azacitidine 75 mg/m^2 as a continuous IV infusion for 7 days on a 28-day cycle for a minimum of 4 cycles. The dose could be adjusted at the beginning of each cycle based on predefined hematology and renal laboratory results. Each subject was monitored throughout the study for response and safety assessments at scheduled intervals. Subjects were continued on therapy until they met criteria for removal from the study, which were

- Achieved CR and received 3 more cycles of treatment
- Failed to demonstrate CR or PR after 16 weeks
- Relapsed
- Diagnosed with AML
- Developed life threatening infection or hemorrhage
- Withdrew due to constraints of the study.

After withdrawal from the study, subjects were to be followed for disease course and survival. Criteria for adverse event recording were not specified in the protocol; however, treatment-related toxicities and complications were to be reported in CALGB Follow-up Forms. Adverse events were collected from CALGB Follow-up Forms for the retrospective analysis.

3.6 Study Population: 45 subjects were planned, 49 subjects were enrolled, and 48 subjects were analyzed. One subject of the 49 was found to have AML (50% blasts in the bone marrow) and was dismissed from the study without taking any medication. Inclusion criteria differ from CALGB 8921 by inclusion of RAEB and RAEB-T only (not CMMoL) and by performance status of 0-3 (not 0-2). Exclusion criteria differ by permitting prior therapy with low dose cytosine arabinoside (prior cytotoxic therapy not permitted in CALGB 8921) and omitting the condition of any other illness that limited survival to <2 years.

3.7 Azacitidine Dose, Dose Adjustment, Method of Administration and Subject Exposure: Subjects received azacitidine 75 mg/m^2 for 7 days as a continuous IV infusion. The drug was mixed fresh every 4 hours and diluted with 50 mL of Ringer's lactate. Subjects repeated the 7-day treatment regimen at 28-day intervals with dose adjustment as needed. This dose was selected on the basis of previous experience with IV azacitidine in more than 800 patients (Von Hoff et al., 1976, ref. 24). The MTD of IV azacitidine was 150 to 200 mg/m^2/day for 5 days every 14 to 28 days, with major toxicities being leukopenia, thrombocytopenia, nausea and vomiting in patients with leukemia, lymphoma or colorectal cancer. In two later studies reported in 1982, the dose of azacitidine as a single agent was 150 m/m^2/day given as a continuous infusion for 5 days.

The mean exposure to azacitidine in the 48 subjects was 7.8 months (range 0.9 to 65.4 months. Twenty patients received <75 mg/m^2/day for 11.7 months, and 28 patients received ≥75 mg/m^2/day for 4.9 months.

3.8 Criteria for Responses and Non-Responses: as in CALGB 9221 trial.

3.9 Subject Disposition: Sponsor's Table 58 summarizes subject disposition. Reasons for withdrawal from therapy are self-explanatory. Follow-up status was obtained from subjects as late a 2873 days (nearly 8 years) after withdrawal from the study. Progression to AML includes the total incidence both on study and after study.

Table 58: Subject Disposition and Completion Status (CALGB 8421)

	Number (%) of Subjects
Disposition Status	**Azacitidine (N=48)**
Received study medication	**48 (100.0)**
Withdrew from therapy	**48 (100.0)**
Reason for withdrawal from therapy[a]	
Achieved complete remission and therapy stopped	3 (6.3)
Development of AML	**5 (10.4)**
Development of a life-threatening infection	**2 (4.2)**
Development of Relapse after PR, CR, or Improvement	**2 (4.2)**
No response to therapy after 4 cycles of treatment	**11 (22.9)**
Adverse event	**10 (20.8)**
Subject did not wish to continue in the study	**4 (8.3)**
Investigator discretion	**2 (4.2)**
Other[b]	**1 (2.1)**
Subject died	**8 (16.7)**
Follow-up status[a]	
Follow-up contact made	**40 (83.3)**
Subject died	**35 (72.9)**
Subject progressed to AML[c]	**14 (29.2)**
Subject diagnosed with another malignancy	**2 (4.2)**
Subject received subsequent radiation therapy	**1 (2.1)**
Subject received subsequent chemotherapy	**19 (39.6)**

[a] Subjects may be categorized to more than 1 reason for withdrawal and follow-up status.
[b] Specified reasons for other are listed by subject and treatment in CALGB 8421 CSR Appendix 16.2.9.13.2.
[c] Total of subjects who progressed to AML includes subjects who were withdrawn from the study due to development of AML.
KEY: AML=acute myelogenous leukemia, CR=Complete Response, PR=Partial Response, CALGB=Cancer and Leukemia Group B

3.10 Protocol Violations: Only 3 /48 subjects had a protocol violation: 2 did not meet MDS eligibility criteria and 1 had prior cytotoxic therapy.

3.11 Subject Demographics: Subject Demographics and Baseline Disease characteristics are shown in Sponsor's Tables 60 and 61.

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Table 60: Subject Demographics (CALGB 8421)

Demographic	Azacitidine (N=48)
Gender (n%)	
Male	31 (64.6)
Female	17 (35.4)
Race (n%)	
White	48 (100.0)
Age (years)	
N	48
Mean ± SD	63.1 ± 10.72
Median	65.0
Range	35 – 81
Age Group (n%)	
Less than 65	21 (43.8)
65 - 74	24 (50.0)
75 and older	3 (6.3)
Height (cm)	
N	42
Mean ± SD	169.6 ± 9.36
Median	168.0
Range	155 – 191
Weight (kg)	
N	43
Mean ± SD	71.7 ± 13.83
Median	[illegible]
Range	49 – 106
BSA (m^2)	
N	45
Mean ± SD	1.82 ± 0.208
Median	1.80
Range	1.46 - 2.20

Values for height, weight and BSA are from baseline vital sign visit.

KEY BSA=body surface area, SD=standard deviation, CALGB=Cancer and Leukemia Group B

Composition of the study population by gender (65% male, 35% female) is consistent with the incidence by gender observed in MDS. All subjects were white. The mean age was 63 years (range 35 to 81 years).

Table 61: Baseline Disease Characteristics (CALGB 8421)

	Number (%) of Subjects
Baseline Disease Characteristic	Azacitidine (N=48)
MDS diagnosis at registration	
RAEB	23 (47.9)
RAEB-T	24 (50.0)
AML	1 (2.1)
Performance status (n %)	
0 Normal	15 (31.3)
1 Fatigue	13 (27.1)
2 Impaired	7 (14.6)
3 Bedrest	3 (6.3)
Unknown/Not Done	10 (20.8)
Transfusion product used in 3 months before study entry	
Any transfusion product	43 (89.6)
Blood cells, packed human	41 (85.4)
Platelets, human blood	16 (33.3)
Unknown	3 (6.3)

Values for performance status are from baseline vital sign visit.

KEY MDS=myelodysplastic syndromes, RAEB=refractory anemia with excess blasts, RAEB-T=refractory anemia with excess blasts in transformation, AML=acute myelogenous leukemia, CALGB=Cancer and Leukemia Group B

RAEB and RAEB-T were about equally represented in the study. Performance status was normal or fatigue in 58% of subjects, but there were some subjects who were impaired or requiring bedrest. About 90% of subjects received transfusions of blood products, mainly RBCs, during 3 months before study entry. Other medical conditions and previous surgeries were common in this study of mostly elderly subjects.

3.12 Primary Efficacy Results

3.12.1 Primary Efficacy Endpoint: Overall Response Rate

The primary endpoint was defined as overall response rate of CR + PR. The best response attained during the study was used to categorize each subject, as shown in sponsor's Table 62.

Table 62: Response Rates of All Subjects (CALGB 8421)

	Number (%) of Subjects
	Azacitidine (N=48)
Response	
Overall (CR + PR)	9 (18.8)
Complete (CR)	3 (6.3)
Partial (PR)	6 (12.5)
Non-response	
Improvement, not CR or PR	11 (22.9)
Stable Disease	27 (56.3)
Disease Progression	0 (0.0)
Unevaluable	1 (2.1)
Total Non-response	39 (81.3)

[illegible] Response [illegible] Response [illegible] and Leukemia Group B

Three of the subjects achieved CR, which occurred from the 5th to the 7th treatment cycle (118 to 230 days on study). Six of the subjects achieved PR, which occurred from the 2nd to the 10th treatment cycle (63 to 281 days on study).

All CR + PR subjects had 2 or 3 cell line abnormality at baseline and all were transfusion dependent.

3.12.2 Duration of Clinical Response

Sponsor's Table 63 presents the data on MDS subtype, abnormalities at baseline, initial positive effect (type and study day), duration of positive effect, best response (type and duration) and last dose. These complex data are presented in part in Reviewer's Table below.

Reviewer's Table. Duration of Positive Effect and of Response in Responders

Initial Positive Effect (Study Day)*	Duration of Positive Effect (days)	Best Response	Duration of CR or PR (days)**
Day 8	342	PR	128
Day 29	316	PR	1
Day 64	421+ (1.2 years)	PR	155
Day 23	427+ (1.2 years)	PR	167+
Day 57	249+	CR	16
Day 9	323	PR	114
Day 9	343+	CR	204
Day 15	49+	PR	1+
Day 11	228+	CR	164+

***First day of achievement of target for ≥4 weeks for at least 1 abnormality at baseline. Duration is number of days until transfusion, relapse, or last observed value.**
****Number of days from first achievement of target for ≥4 weeks for all baseline abnormalities until sustained loss of target values.**

The mean and median duration of response was 106 days and 128 days. The mean and median duration of positive effect was 300 days and 323 days, or nearly

3 times longer than that of response. The actual durations of response or positive effect were probably artificially shortened for several subjects because of withdrawals from the study.

Reviewer's Notes: A review of PATIENT PROFILES showed that:

- *The median duration of response could only be estimated, as the response was continuing in all (100%) patients at the time of their withdrawal from the study.*
- *The median duration was 281 + days, the mean duration was 389 + days, the range was 84 days to 1499 + days.*

3.12.3 Response Rate by MDS Subtype

Response rates by MDS subtype are shown in Reviewer's Table below (data from sponsor's Table 64). Response rates in RAEB and in RAEB-T were about the same.

Response Rates of All Subjects by MDS Subtypes and AML at Baseline

MDS Subtype and Response	Number of Subjects	% of Subjects with Subtype
RAEB	**N=23**	**100%**
• **CR + PR**	**4**	**17.4%**
• **CR**	**1**	
• **PR**	**3**	
RAEB-T	**N=24**	**100%**
• **CR + PR**	**5**	**20.8%**
• **CR**	**2**	
• **PR**	**3**	
AML	**N=1**	
• **CR + PR**	**0**	

3.12.4 Response Rates Excluding Subjects with Baseline Diagnosis of AML, Subjects with Protocol Violations, and Applying ≥4-Week Duration Requirement

Exclusion of the one subject with baseline diagnosis of AML did not change the response rate (19.1%). Exclusion of 3 subjects with protocol violations increased the response rate slightly to 20%.

The protocol for CALGB 8421, unlike those for CALGB 8921 and CALGB 9221, did not require targets to be maintained for 4 weeks to be assessed as response. The requirement for response was only that all abnormalities at baseline must achieve the response criteria for 1 day. Sponsor's Table 66, shown below, presents adjusted response rates for CALGB 8421 according to response criteria used in CALGB 8921 and CALGB 9221.

Table 66: Adjusted Overall Response Rate ≥ 4 Weeks Duration (CALGB 8421)

Response	Number (%) of Subjects Azacitidine (N=48)
Overall (CR + PR)	7 (14.6)
Complete (CR)	2 (4.2)
Partial (PR)	5 (10.4)

KEY: CR=Complete Response, PR=Partial Response, CALGB=Cancer and Leukemia Group B

The adjusted response rate was 14.6%.

3.12.5 Evidence of Clinical Benefit: Improvement

Of the 48 subjects, 23% (11/48) had the best response of Improvement.

- All 11 were anemic and 9 were RBC transfusion dependent. Eight of 11 lost transfusion dependence, 5 of them had a ≥50% increase in Hgb, 3 of them had <50% increase in Hgb.
- Nine of 11 subjects were thrombocytopenic, as specified in the protocol. All 9 subjects increased platelet counts by ≥50%.
- Seven of 11 subjects had lower than normal WBC counts. Six of 11 increased WBC counts by ≥50% and 1 by <50%.

These changes are summarized in Reviewer's Table below (data from Sponsor's Table 67).

Reviewer's Table. Best Response of Improvement

Peripheral Blood Cells	Abnormal at Baseline	Positive Change	≥50% Increase and Transfusion Free	<50% Increase and Transfusion Free
Hgb	**11/11**	**8/11 (73%)**	**5/11**	**3/11**
Platelets	**9/11**	**9/9 (100%)**	**9/9**	**0**
WBC	**7/11**	**7/7 (100%)**	**6/7**	**1/7**

Reviewer's Note: a Review of PATIENT PROFILES showed that:

- *8 patients met the criteria for improvement (See Appendix for the list of patients with Improvement according to the sponsor and according to the Reviewer),*
- *5 continued in Improved status at the time of withdrawal from the study; 3 reverted to pre-Improved status,*
- *The median duration was estimated as 145 + days, the mean duration as 191 + days, the range 42 to 570 days.*

3.12.6 Analyses of Response Rates by Age and Gender

These analyses are presented in sponsor's Tables 68 and 69, and are summarized in the Reviewer's Table below. Only response rates are presented; non-response rates are not reproduced.

Reviewer's Table. Response Rates by Age and Gender

Parameter		Overall CR + PR	CR	PR
Age:	<65 years	6/21 (29%)	2	4
	65 – 74	3/27 (11%)	1	2
	≥75	1/3 (33%)	1	0
Gender:	Male	5/31 (16%)	1	4
	Female	4/17 (24%)	2	2

D. Efficacy Conclusions

1. Efficacy of azacitidine in inducing prolonged responses, with complete or partial normalization of peripheral blood counts and bone marrow blast percentages and with decrease or elimination of transfusion dependence, in patients with all MDS subtypes is summarized in Reviewer's Table below. A total of 270 subjects were treated with the same dose of azacitidine, SC in CALGB 9221 and 8921 trials and IV in CALGB 8421 trial. The overall response rate was 15.2%.

Reviewer's Table. Summary of Azacitidine Efficacy in MDS (ITT Population)

Response	CALGB 9221 All Azacitidine N=150	CALGB 8921 N=72	CALGB 8421 N=48	Total N=270
Overall (CR + PR)	22 (14.7%)	10 (13.9%)	9 (18.8%)	41 (15.2%)
CR	9	4	3	16
PR	13	6	6	25

After exclusion of 28 patients adjudicated to have AML, these statistics change only slightly, since 5 of the AML patients (17.9%) had CR or PR. Response rates after exclusion of patients adjudicated to have AML are shown in Reviewer's Table below. In the 3 trials, 36 of 238 MDS subjects had complete or partial responses, for a response rate of 15.1%.

Reviewer's Table. Summary of Azacitidine Response Rates in MDS After Excluding Subjects with Adjudicated Diagnosis of AML at Study Entry

Response	CALGB 9221 All Azacitidine N=136	CALGB 8921 N=55	CALGB 8421 N=47	Total N=238
Overall (CR + PR)	20 (14.7%)	7 (12.7%)	9 (19.1%)	36 (15.1%)
CR	8	3	3	14
PR	12	4	6	22

2. The response rates in the 3 trials were similar (12.7% to 19.1%), suggesting that this degree of efficacy is reproducible. The responses were not spurious, as there were 0% responses in CALGB 9221 Observation Only without

Crossover control arm. The difference between azacitidine-treated subjects and the Observation without Crossover control subjects in CALGB 9221 trial was statistically significant for overall response rate ($p<0.0001$).

3. Analysis of response rates by dose showed that 75 mg/m^2 was an effective starting dose. Doses were decreased to <75 mg/m^2 or increased to >75 mg/m^2 based on each subject's response. The highest administered doses of azacitidine in each study were 150 mg/m^2 received by 2 subjects in CALGB 8421, 100mg/m^2 received by 2 subjects in CALGB 8921, and 100mg/m^2 received by 3 subjects in CALGB 9221. Reviewer's Table below shows the combined data of all 3 CALGB trials (data from sponsor's Table 72). Most subjects with a best response of CR or PR received 75 mg/m^2 for the majority of cycles prior to response.

Reviewer's Table. Response Rates As A Function of Azacitidine Dose

Response	All Azacitidine <75 mg/m^2 N=44	All Azacitidine ≥75 to <100 mg/m^2 N=190	All Azacitidine ≥100 mg/m^2 N=15
Overall (CR + PR)	15 (34%)	19 (10%)	7 (47%)
CR	6	7	3
PR	9	12	4

4. The responses were long lasting in most patients. The duration of responses is underestimated, since over 70% of subjects were still in response at the time of withdrawal from the trials.
5. Long-term administration of azacitidine is possible, as demonstrated by 3 patients who continued to receive azacitidine for 15, 68 and 156 cycles, respectively, instead of discontinuing it after 3 cycles following CR.
6. In addition to CR and PR responses, lesser responses not meeting PR criteria, termed Improvement occurred in 20.0% of azacitidine-treated patients and in 0% of observation only without crossover patients in CALGB 9221 trial. Improvement occurred in 8.3% of subjects in CALGB 8921 trial and in 16.7% of subjects in CALGB 8421 trial. In the 3 trials, the mean percentage of azacitidine-treated subjects with Improvement was 16.3%. Most of the subjects with Improvement who were transfusion dependent at baseline became free of the need for RBC or platelet transfusions for the period of Improvement. The median duration of Improvement in azacitidine-treated patients in the 3 trials was 195 days.
7. Response rates were similar in subjects with all MDS subtypes and with AML.
8. Follow-ups in all three trials were as long as 8 years after subject withdrawal, and the percentage of subjects followed up was between 80% and 90%.

Efficacy evaluation is confounded several considerations:

1. The primary trial data were no longer available and were re-collected from patient records by the sponsor. This is an unusual procedure for an NDA submission, as the data cannot be easily verified. However, the trials were

conducted under NCI/CALGB auspices and the results were published, lending credence to the data in the submission.

2. The design of the pivotal controlled trial permitted crossover from the observation arm to the azacitidine arm after pre-specified criteria were met. More than one-half of the subjects crossed over to azacitidine treatment, but remained in the control arm in statistical analysis. The crossover patients had a response rate similar to that of subjects randomized to azacitidine, and therefore the difference between azacitidine treatment and observation was not statistically different. Clearly, this analysis misrepresents the efficacy of azacitidine, because the only subjects who had a response had been treated with azacitidine.
3. The statistical plan for CALGB 9221 trial, in calculating the sample size for the trial, made an assumption of a 20% difference between azacitidine response rate and control (30% and 10%). This assumption proved to be too optimistic.
4. The statistical reviewer concluded that the results of the one controlled, randomized Phase 3 study, CALGB 9221, are not adequate to support the sponsor's efficacy claim, since they are based on retrospective statistical design, retrospective data collection and analyses. The study appears to demonstrate a significant benefit for the overall response of azacitidine compared to observation before crossover group for ITT population ($p<0.0001$), ITT population without AML at study entry ($p<0.0001$), and ITT population without AML or protocol violation ($p=0.0007$). It also appears to demonstrate a significant benefit of azacitidine compared to observation only group (excluding crossover patients) for ITT population ($p=0.0033$), ITT population without AML ($p=0.010$), and ITT population without AML or protocol violation ($p=0.0276$).

Nevertheless, in absence of an effective drug for MDS, a reproducible 15% response rate to azacitidine is a valuable addition to armamentarium. For this reason and for separation of true control group from the azacitidine group in analysis of the results, FDA suggested separating the Observation Without Crossover subjects from Azacitidine After Observation subjects. As a result,

- Response rates for all azacitidine-treated subjects could be calculated, and
- The absence of responses in the Observation Only group was established.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

1. This NDA documents the safety profile of azacitidine in 226 subjects, 220 of them in the 3 clinical trials and 6 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.
2. The same dose of azacitidine was used in the 3 clinical trials (IV in one trial and SC in two trials, including the controlled pivotal trial).
3. There were no deaths in these trials that were attributed to azacitidine toxicity. Serious adverse events occurred in about 60% of azacitidine-treated patients

and in about 36% of observation only patients. The most common SAEs were thrombocytopenia, febrile neutropenia, fever and pneumonia.

4. Virtually all subjects reported adverse events during the study, both in the azacitidine-treated subjects and in the observation only subjects. A greater proportion of azacitidine-treated subjects reported the following adverse events as compared to observation only subjects: gastrointestinal events (nausea, vomiting, diarrhea, constipation, anorexia), hematologic events (neutropenia, leukopenia, fever, rigors, ecchymoses, patechia, epistaxis), injection site events (erythema, bruising and pain), cough, dyspnea, arthralgia, headache, weakness, dizziness and insomnia.
5. Subjects reported the most TEAEs in the first 2 cycles of azacitidine therapy and progressively fewer in subsequent cycles.
6. The most common reasons for azacitidine discontinuation, dose reduction or therapy interruption were leukopenia, neutropenia, thrombocytopenia.
7. The most common conditions treated in the azacitidine treatment subjects were nausea, vomiting, fever, constipation, diarrhea and hypokalemia. The most common conditions treated in the observation only group were fever, hypokalemia and nausea.
8. Blood cell counts were low at baseline in all subjects and decreased in subjects treated with azacitidine. Blood counts increased in subjects who showed a response or improvement. Liver function TEAEs coincided with intercurrent illnesses, including hepatobiliary disorders. Three patients developed increased hepatic impairment during azacitidine treatment; two of them had been previously diagnosed with cirrhosis of the liver. Renal TEAEs were rare, transient and attributed to concomitant conditions. Five azacitidine-treated patients and 1 observation only patient developed renal failure in a variety of settings, such as sepsis, hypotension, hypertension, diabetes mellitus and heart failure.
9. Gastrointestinal TEAEs tended to increase with increasing dose of azacitidine. Other events were less dose-related, such as anemia, erythema, ecchymosis, weakness, dyspnea, site pain and arthralgia. Most types of TEAEs were unrelated to dose.
10. 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.

B. Description of Patient Exposure

1. Number of Subjects: 226 subjects were exposed to SC azacitidine, 54 to IV azacitidine and 41 served as controls in the controlled trial, as shown in Reviewer's Table below.

Reviewer's Table. Overall Extent of Exposure to Azacitidine, All Subjects

Study number	Azacitidine SC	Azacitidine IV	Controls to azacitidine treatment
AZA-2002-BA-002	6*	6*	-
CALGB 9221	150	-	41
CALGB 8921	70	-	-
CALGB 8421	-	48	-
Total	226	54	41

*6 subjects received one dose SC and one dose IV.

Study AZA-2002-BA-002 was a multicenter, randomized, open-label, two-treatment, two-period, crossover study conducted to assess the bioavailability of SC and IV azacitidine in 6 subjects with MDS. Each patient received single doses of 75 mg/m^2 azacitidine SC and IV infusion administered over 10 minutes, with at least 7 days between doses. Each of the 2 treatment periods lasted approximately 3 days, with a minimum of 7 days and maximum of 28 days between doses. Pharmacokinetic sample collection and safety assessments were performed during each treatment period. Serial plasma samples were collected from predose until 48 hours after the beginning of each dose. For subjects who entered the study after protocol amendment 2, pharmacokinetic samples were not collected at 24 and 48 hours postdose. Safety evaluations were repeated 10 $\pm$3 days after the last dose.

The CALGB studies 9221, 8921 and 8421 were described above in the Efficacy section.

2. Duration of Exposure by Cycle

The duration of exposure to azactidine is presented below in the sponsor's Table 3 in ISS (Integrated Summary of Safety).

Table 3: Duration of Exposure by Cycle

	Number (%) of Subjects			
	Intravenous	Subcutaneous		
	8421	8921	9221	8921/9221
Cycle Category	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine* (N=150)	All Azacitidine* (N=220)
Cycles 1 or more	48 (100.0)	70 (100.0)	150 (100.0)	220 (100.0)
Cycles 6 or more	17 (35.4)	25 (35.7)	74 (49.3)	99 (45.0)
Cycles 12 or more	9 (18.8)	13 (18.6)	38 (25.3)	51 (23.2)
Cycles 24 or more	1 (2.1)	2 (2.9)	14 (9.3)	16 (7.3)

* All Azacitidine: Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

Data Source: Table 15-49

In the above table, subjects who were exposed to IV azacitidine are tabulated separately from those who received SC azacitidine. In the two earlier trials (8421 and 8921) about 36% of subjects received azacitidine for 6 cycles or more, and

about 19% received azacitidine for 12 cycles or more. This statistic is remarkable because patients who did not respond to 4 cycles of therapy were supposed to be discontinued, as well as patients who achieved a CR and had 3 additional cycles of therapy. The exposure is even greater in the 9221 trial, in which 49% of subjects randomized to azacitidine and crossover subjects from Observation Only received azacitidine for 6 cycles or more, 25% for 12 cycles or more, and 9% for 24 cycles or more.

The average cycle length for all studies was about 34 days, the average number of days dosed was about 6.9, the average daily dose by BSA was 69.5 mg/m^2 (median dose 75.0 mg/m^2, minimum dose 31.2 mg/m^2, maximum dose 99.7 mg/m^2), and the average total daily dose was 130 mg/m^2 (median dose 131.0 mg/m^2, minimum dose 49.9 mg/m^2, maximum dose 238.8 mg/m^2). These parameters were virtually identical for IV doses and for SC doses.

The extent of exposure by dose is shown in sponsor's Table 6 (from ISS).

Table 6: Extent of Exposure by Dose

	Number (%) of Subjects							
	Intravenous		Subcutaneous					
	8421		8921		9221		8921/9221	
Dose	Azacitidine (N=48)		Azacitidine (N=70)		All Azacitidine[a] (N=150)		All Azacitidine[a] (N=220)	
<75 mg/m^2	20	(41.7)	24	(34.3)	76	(50.7)	100	(45.5)
≥75 to <100 mg/m^2	46	(95.8)	69	(98.6)	149	(99.3)	218	(99.1)
≥100 mg/m^2	12	(25.0)	18	(25.7)	19	(12.7)	37	(16.8)

[a] All Azacitidine. Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

Data Source: 8421 CSR, Appendix 16.2.8.1 and Table 15-38

Virtually all subjects received doses of ≥75 mg/m^2 to <100 mg/m^2. About one-half (51%) of the subjects in the 9221 trial and 34% - 42% of subjects in 8921 and 8421 trials experienced dose reductions to <75 mg/m^2, and 13% to 25% of subjects experienced dose escalations to ≥100 mg/m^2.

The sponsor also calculated the total exposure to azacitidine for all subjects in subject-years, shown in sponsor's Table 7 (ISS). These statistics show that the total exposure was longer in study 9221 (0.92 years per subject) than in studies 8921 (0.74 years per subject) and 8421 (0.59 years per subject).

Table 7: Total Exposure in Subject-Years

	Total Exposure (Subject-years)				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Statistic	Azacitidine[a] (N=49)	Azacitidine[a] (N=72)	All Azacitidine[a,b] (N=150)	Observation[c] (N=92)	All Azacitidine[a,b] (N=222)
N	48	70	150	92	220
Sum	28.5	53.2	138.2	43.2	191.4

[a] Azacitidine therapy duration: Time from first dose to end of study (30 days after last dose).

[b] All Azacitidine: Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

[c] Observation therapy duration: Time from randomization to withdrawal from study or day prior to crossover.

Data Source: Table 15-2

3. Patients Who Discontinued Study Treatment

Sponsor's Table 8 (ISS) summarizes the disposition of all subjects in the 3 trials. Virtually all subjects who received azacitidine SC (220) and IV (48) are accounted for. One subject in study 8421 and two in study 8921 were withdrawn from the study before receiving study drug. Two subjects (one in study 8921 and one in the observation arm of study 9221) did not have completion status, because they were still in the study at the time of last contact. One had a CR (in study 8921) and one had stable disease (in study 9221).

Table 8: Subject Disposition and Completion Status

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Disposition Status	Azacitidine (N=49)	Azacitidine (N=72)	All Azacitidine[a] (N=150)	Observation without crossover (N=41)	All Azacitidine[a] (N=222)
Randomized or registered	49	72	150	41	222
Received study medication	48 (98.0)[c]	70 (97.2)[c]	150(100.0)	0 (0.0)	220 (99.1)
Withdrew from therapy/observation	49(100.0)	71 (98.6)[d]	150(100.0)	40 (97.6)[d]	221 (99.5)
Reason(s) for withdrawal from therapy/observation[b]					
No response after 4 cycles of treatment	11 (22.4)	9 (12.5)	30 (20.0)	0 (0.0)	39 (17.6)
Development of AML	5 (10.2)	12 (16.7)	20 (13.3)	18 (43.9)	32 (14.4)
Adverse event	10 (20.4)	18 (25.0)	13 (8.7)	1 (2.4)	31 (14.0)
Subject did not wish to continue in study	4 (8.2)	5 (6.9)	25 (16.7)	2 (4.9)	30 (13.5)
Other	1 (2.0)	6 (8.3)	24 (16.0)	10 (24.4)	30 (13.5)
Subject died	8 (16.3)	8 (11.1)	20 (13.3)	6 (14.6)	28 (12.6)
Investigator discretion	2 (4.1)	3 (4.2)	18 (12.0)	1 (2.4)	21 (9.5)
Achieved CR and therapy stopped	3 (6.1)	5 (6.9)	8 (5.3)	0 (0.0)	13 (5.9)
Development of relapse after PR, CR, or improvement	2 (4.1)	4 (5.6)	3 (2.0)	0 (0.0)	7 (3.2)
Completed treatment per protocol	0 (0.0)	1 (1.4)	4 (2.7)	0 (0.0)	5 (2.3)
No reason given	1 (2.0)	1 (1.4)	1 (0.7)	1 (2.4)	2 (0.9)
Poor compliance	0 (0.0)	1 (1.4)	0 (0.0)	1 (2.4)	1 (0.5)
Subject is lost to follow-up	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.5)
Development of a life-threatening infection	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Development of a life-threatening hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Development of new malignancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] All Azacitidine: Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

[b] Reason for withdrawal: Subjects may be categorized to more than 1 reason for withdrawal.

[c] One subject (Subject 36482) in the 8421 study and 2 subjects (Subjects 44413 and 44414) in the 8921 study were withdrawn from the study before receiving study drug.

[d] One subject (Subject 44413) in the 8921 study and 1 subject (Subject 58418) in the 9221 observation without crossover group did not have a completion status available because the subjects remained in the study at the time of last contact.

KEY: AML=acute myelogenous leukemia, CR=complete response, PR=partial response

Data Source: Table 15-3

The frequencies of reasons for withdrawal were similar between the IV and SC azacitidine groups. The most common reasons were 1) no response after 4 cycles of treatment, 2) development of AML, 3) adverse event (20% - 25% in Studies 8421 and 8921 and only 9% in Study 9221), and 4) death. Subjects' decision to discontinue in the study was more common (17%) in study 9221 than in Studies 8421 and 8921 (7% - 8%).

Subjects in the Observation Only group more commonly progressed to AML (44% vs. 13%) than the azacitidine groups. They rarely withdrew because of adverse event(s) (2% vs. 9% - 25%), but more commonly (24% vs. 2% to 14%) for "Other reasons", which included loss of efficacy and administrative reasons, than subjects in the azacitidine groups.

Follow-up status was obtained from 80% to 90% of subjects in the three groups (a later listing submitted by the sponsor accounts for deaths of 190/191 subjects in the 9221 trial, the remaining subject still alive at last contact). Therefore, sponsor's Table 9, shown below, is incomplete.

Table 9: Follow-up Status

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Follow-up Status[a]	Azacitidine (N=49)	Azacitidine (N=72)	All Azacitidine[b] (N=150)	Observation without crossover (N=41)	All Azacitidine[b] (N=222)
Follow-up contact made	40 (81.6)	64 (88.9)	129 (86.0)	35 (85.4)	193 (86.9)
Subject died	35 (71.4)	62 (86.1)	122 (81.3)	33 (80.5)	184 (82.9)
Subject progressed to AML	14 (28.6)	32 (44.4)	57 (38.0)	21 (51.2)	89 (40.1)
Subject received subsequent chemotherapy	19 (38.8)	26 (36.1)	58 (38.7)	27 (65.9)	84 (37.8)
Subject diagnosed with another malignancy	2 (4.1)	4 (5.6)	4 (2.7)	3 (7.3)	8 (3.6)
Subject received subsequent radiation therapy	1 (2.0)	3 (4.2)	5 (3.3)	1 (2.4)	8 (3.6)

[a] Follow-up status: Subjects may be categorized to more than 1 category for follow-up status.
[b] All Azacitidine: Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.
Key: AML=acute myelogenous leukemia
Data Source: Table 15-3

Nevertheless, the conclusions are that more subjects in the observation group progressed to AML, received subsequent chemotherapy, and were diagnosed with a second malignancy than subjects in the azacitidine groups.

4. Demographic, Baseline and MDS Subtype Characteristics were described above under each trial.

C. Methods and Specific Findings of Safety Review

1. Non-Treatment-Emergent Adverse Events (Non-TEAEs)

Non-TEAEs are adverse events that occurred with an onset prior to the date of randomization or more than 30 days after the last dose of azacitidine or, in the case of observation only subjects, after withdrawal from the study. Non-TEAEs are background events in subjects with MDS and occurred with about equal frequency in the observation only group and in all azacitidine groups. Almost one-third of the subjects in each group had at least one non-TEAE, and as would be expected in this population, anemia, thrombocytopenia, fever and neutropenia were most frequent. Sponsor's Table 13 (ISS) demonstrates the incidence of non-TEAEs occurring in 5% of any treatment group.

Table 13: Non-TEAEs Occurring in ≥ 5.0% in Any Treatment Group

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Preferred Term[a]	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[b] (N=150)	Observation (N=92)	All Azacitidine[b] (N=220)
At least 1 non-TEAE	16 (33.3)	16 (22.9)	47 (31.3)	30 (32.6)	63 (28.6)
Anemia NOS	3 (6.3)	5 (7.1)	17 (11.3)	16 (17.4)	22 (10.0)
Thrombocytopenia	4 (8.3)	4 (5.7)	12 (8.0)	12 (13.0)	16 (7.3)
Pyrexia	1 (2.1)	2 (2.9)	6 (4.0)	8 (8.7)	8 (3.6)
Neutropenia	1 (2.1)	2 (2.9)	5 (3.3)	7 (7.6)	7 (3.2)
Leukopenia NOS	5 (10.4)	1 (1.4)	5 (3.3)	4 (4.3)	6 (2.7)
Diarrhea NOS	0	0	5 (3.3)	5 (5.4)	5 (2.3)
Hypokalemia	2 (4.2)	1 (1.4)	2 (1.3)	5 (5.4)	3 (1.4)
Rigors	1 (2.1)	0	2 (1.3)	5 (5.4)	2 (0.9)
Appetite decreased NOS	0	0	0	5 (5.4)	0
Headache NOS	1 (2.1)	0	0	5 (5.4)	0

[a] Multiple reports of the same preferred term for a subject are only counted once within each treatment group.
[b] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.
Sorted by decreasing frequency in the 8921/9221 all azacitidine group.
KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event
Data Source: Table 15-8

2. Treatment-Emergent Adverse Events (TEAEs)

Sponsor's Table 14 lists system organ class (SOC) TEAEs by treatment group. Virtually all subjects in azacitidine treatment groups and in the observation group reported at least 1 TEAE. The observation group consisted of observation only subjects until withdrawal or until crossover to azacitidine (footnote to Table 15-11, the source for this table). The incidence of most adverse events, except blood and lymphatic system disorders, in the observation group is lower by 30% - 50% than that in azacitidine groups.

All TEAEs sorted by decreasing frequency are shown below in sponsor's Table 15. The cutoff in this table is events occurring in 20% of patients. A table with a cutoff of 5% is shown in the Appendix.

Table 14: SOCs From Which TEAEs Were Most Frequently[a] Reported

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
System Organ Class[b]	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[c] (N=150)	Observation (N=92)	All Azacitidine[c] (N=220)
At least 1 TEAE	48(100.0)	69 (98.6)	150(100.0)	89 (96.7)	219 (99.5)
Blood and lymphatic system disorders	43 (89.6)	68 (97.1)	143 (95.3)	78 (84.8)	211 (95.9)
General disorders and administration site conditions	44 (91.7)	65 (92.9)	139 (92.7)	59 (64.1)	204 (92.7)
Gastrointestinal disorders	46 (95.8)	65 (92.9)	136 (90.7)	46 (50.0)	201 (91.4)
Respiratory, thoracic and mediastinal disorders	40 (83.3)	50 (71.4)	110 (73.3)	47 (51.1)	160 (72.7)
Skin and subcutaneous tissue disorders	39 (81.3)	54 (77.1)	104 (69.3)	41 (44.6)	158 (71.8)
Infections and infestations	35 (72.9)	47 (67.1)	89 (59.3)	41 (44.6)	136 (61.8)
Musculoskeletal and connective tissue disorders	28 (58.3)	42 (60.0)	89 (59.3)	28 (30.4)	131 (59.5)
Nervous system disorders	33 (68.8)	33 (47.1)	80 (53.3)	26 (28.3)	113 (51.4)
Vascular disorders	30 (62.5)	39 (55.7)	73 (48.7)	24 (26.1)	112 (50.9)
Investigations	28 (58.3)	34 (48.6)	69 (46.0)	31 (33.7)	103 (46.8)
Metabolism and nutrition disorders	30 (62.5)	36 (51.4)	61 (40.7)	25 (27.2)	97 (44.1)
Injury, poisoning, and procedural complications	19 (39.6)	29 (41.4)	52 (34.7)	15 (16.3)	81 (36.8)
Psychiatric disorders	24 (50.0)	28 (40.0)	51 (34.0)	13 (14.1)	79 (35.9)
Cardiac disorders	20 (41.7)	21 (30.0)	53 (35.3)	16 (17.4)	74 (33.6)
Renal and urinary disorders	22 (45.8)	16 (22.9)	37 (24.7)	11 (12.0)	53 (24.1)
Eye disorders	19 (39.6)	14 (20.0)	31 (20.7)	2 (2.2)	45 (20.5)
Hepatobiliary disorders	14 (29.2)	7 (10.0)	16 (10.7)	6 (6.5)	23 (10.5)

[a] ≥ 20.0% frequency in any treatment group.

[b] Multiple reports of the same system organ class for a subject are only counted once within each treatment group.

[c] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

Sorted by decreasing frequency in the 8921/9221 all azacitidine group.

KEY: SOC=system organ class, TEAE=treatment-emergent adverse event

Data Source: Table 15-9

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Table 15: Most Frequently[a] Observed TEAEs

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Preferred Term[b]	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[c] (N=150)	Observation (N=92)	All Azacitidine[c] (N=220)
At least 1 TEAE	48(100.0)	69 (98.6)	150(100.0)	89 (96.7)	219 (99.5)
Nausea	31 (64.6)	55 (78.6)	100 (66.7)	16 (17.4)	155 (70.5)
Anemia NOS	37 (77.1)	46 (65.7)	107 (71.3)	59 (64.1)	153 (69.5)
Thrombocytopenia	34 (70.8)	42 (60.0)	102 (68.0)	42 (45.7)	144 (65.5)
Vomiting NOS	26 (54.2)	47 (67.1)	72 (48.0)	5 (5.4)	119 (54.1)
Pyrexia	29 (60.4)	37 (52.9)	77 (51.3)	28 (30.4)	114 (51.8)
Leukopenia NOS	29 (60.4)	30 (42.9)	76 (50.7)	27 (29.3)	106 (48.2)
Diarrhea NOS	22 (45.8)	26 (37.1)	54 (36.0)	13 (14.1)	80 (36.4)
Fatigue	13 (27.1)	21 (30.0)	59 (39.7)	23 (25.0)	79 (35.9)
Injection site erythema	0	28 (40.0)	49 (32.7)	0	77 (35.0)
Constipation	17 (35.4)	16 (22.9)	58 (38.7)	6 (6.5)	74 (33.6)
Neutropenia	7 (14.6)	20 (28.6)	51 (34.0)	10 (10.9)	71 (32.3)
Ecchymosis	16 (33.3)	23 (32.9)	44 (29.3)	14 (15.2)	67 (30.5)
Cough	10 (20.8)	18 (25.7)	47 (31.3)	14 (15.2)	65 (29.5)
Weakness	17 (35.4)	20 (28.6)	44 (29.3)	19 (20.7)	64 (29.1)
Dyspnea NOS	14 (29.2)	17 (24.3)	47 (31.3)	11 (12.0)	64 (29.1)
Rigors	17 (35.4)	17 (24.3)	39 (26.0)	10 (10.9)	56 (25.5)
Petechiae	22 (45.8)	23 (32.9)	29 (19.3)	8 (8.7)	52 (23.6)
Injection site pain	0	14 (20.0)	36 (24.0)	0	50 (22.7)
Arthralgia	14 (29.2)	13 (18.6)	36 (24.0)	3 (3.3)	49 (22.3)
Headache NOS	11 (22.9)	14 (20.0)	34 (22.7)	10 (10.9)	48 (21.8)
Anorexia	7 (14.6)	13 (18.6)	32 (21.3)	6 (6.5)	45 (20.5)
Pharyngitis	9 (18.8)	12 (17.1)	32 (21.3)	7 (7.6)	44 (20.0)
Pain in limb	6 (12.5)	10 (14.3)	34 (22.7)	5 (5.4)	44 (20.0)
Edema peripheral	12 (25.0)	13 (18.6)	28 (18.7)	10 (10.9)	41 (18.6)
Dizziness	8 (16.7)	15 (21.4)	26 (17.3)	5 (5.4)	41 (18.6)
Contusion	7 (14.6)	10 (14.3)	31 (20.7)	9 (9.8)	41 (18.6)
Erythema	10 (20.8)	14 (20.0)	23 (15.3)	4 (4.3)	37 (16.8)
Epistaxis	11 (22.9)	11 (15.7)	25 (16.7)	9 (9.8)	36 (16.4)
Rash NOS	6 (12.5)	14 (20.0)	17 (11.3)	9 (9.8)	31 (14.1)
Injection site bruising	0	15 (21.4)	16 (10.7)	0	31 (14.1)
Anxiety	8 (16.7)	16 (22.9)	13 (8.7)	3 (3.3)	29 (13.2)
Hypokalemia	15 (31.3)	8 (11.4)	20 (13.3)	12 (13.0)	28 (12.7)
Appetite decreased NOS	11 (22.9)	8 (11.4)	20 (13.3)	8 (8.7)	28 (12.7)
Insomnia	11 (22.9)	6 (8.6)	18 (12.0)	4 (4.3)	24 (10.9)
Rales	11 (22.9)	7 (10.0)	12 (8.0)	8 (8.7)	19 (8.6)
Cellulitis	10 (20.8)	5 (7.1)	13 (8.7)	4 (4.3)	18 (8.2)

[a] ≥ 20.0% frequency in any treatment group.
[b] Multiple reports of the same preferred term for a subject are only counted once within each treatment group.
[c] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.
Sorted by decreasing frequency in the 8921/9221 all azacitidine group.
KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event

Again, the Observation group has a lower incidence of most TEAEs than azacitidine group. Notably less frequent are:

- Nausea, vomiting, diarrhea, constipation, anorexia
- Fever, rigors, leukopenia, neutropenia
- Injection site erythema, bruising and pain
- Ecchymosis, patechiae, contusion, erythema, epistaxis
- Cough, dyspnea
- Arthralgia, headache, weakness, pain in limb, dizziness, and insomnia.

The mean duration of exposure was two-fold longer in azacitidine subjects compared to observation subjects. To address the imbalance of duration of exposure, the sponsor calculated the incidence of TEAEs by subject-years of

exposure (sponsor's Table 17). The incidence of TEAEs was calculated in subjects exposed to azacitidine, from the first dose to 30 days after the last dose, and in observation subjects, from time of randomization to withdrawal from study or to day prior to crossover.

Table 17: Most Frequently[a] Observed TEAEs by Subject-Years of Exposure

	Number of Subjects (Number of subjects with events per subject-year of exposure)				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Preferred Term[b]	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[c] (N=150)	Observation (N=92)	All Azacitidine[c] (N=220)
Total exposure (subject-years)[d]	28.5	53.2	138.2	43.2	191.4
At least 1 TEAE	48 (1.68)	69 (1.30)	150 (1.09)	85 (2.06)	219 (1.14)
Nausea	31 (1.09)	55 (1.03)	100 (0.72)	16 (0.37)	155 (0.81)
Anemia NOS	37 (1.30)	46 (0.86)	107 (0.77)	59 (1.37)	153 (0.80)
Thrombocytopenia	34 (1.19)	42 (0.79)	102 (0.74)	42 (0.97)	144 (0.75)
Vomiting NOS	26 (0.91)	47 (0.88)	72 (0.52)	5 (0.12)	119 (0.62)
Pyrexia	29 (1.02)	37 (0.70)	77 (0.56)	28 (0.65)	114 (0.60)
Leukopenia NOS	29 (1.02)	30 (0.56)	76 (0.55)	27 (0.63)	106 (0.55)
Diarrhea NOS	22 (0.77)	26 (0.49)	54 (0.39)	13 (0.30)	80 (0.42)
Fatigue	13 (0.46)	21 (0.39)	58 (0.42)	23 (0.53)	79 (0.41)
Injection site erythema	0	28 (0.53)	49 (0.35)	0	77 (0.40)
Constipation	17 (0.60)	16 (0.30)	58 (0.42)	6 (0.14)	74 (0.39)
Neutropenia	7 (0.25)	20 (0.38)	51 (0.37)	10 (0.23)	71 (0.37)
Ecchymosis	16 (0.56)	23 (0.43)	44 (0.32)	14 (0.32)	67 (0.35)
Cough	10 (0.35)	18 (0.34)	47 (0.34)	14 (0.32)	65 (0.34)
Weakness	17 (0.60)	20 (0.38)	44 (0.32)	19 (0.44)	64 (0.33)
Dyspnea NOS	14 (0.49)	17 (0.32)	47 (0.34)	11 (0.25)	64 (0.33)
Rigors	17 (0.60)	17 (0.32)	39 (0.28)	10 (0.23)	56 (0.29)
Petechiae	22 (0.77)	23 (0.43)	29 (0.21)	8 (0.19)	52 (0.27)
Injection site pain	0	14 (0.26)	36 (0.26)	0	50 (0.26)
Arthralgia	14 (0.49)	13 (0.24)	36 (0.26)	3 (0.07)	49 (0.26)
Headache NOS	11 (0.39)	14 (0.26)	34 (0.25)	10 (0.23)	48 (0.25)
Anorexia	7 (0.25)	13 (0.24)	32 (0.23)	6 (0.14)	45 (0.24)
Pharyngitis	9 (0.32)	12 (0.23)	32 (0.23)	7 (0.16)	44 (0.23)
Pain in limb	6 (0.21)	10 (0.19)	34 (0.25)	5 (0.12)	44 (0.23)
Edema peripheral	12 (0.42)	13 (0.24)	28 (0.20)	10 (0.23)	41 (0.21)
Dizziness	8 (0.28)	15 (0.28)	26 (0.19)	5 (0.12)	41 (0.21)
Contusion	7 (0.25)	10 (0.19)	31 (0.22)	9 (0.21)	41 (0.21)
Erythema	10 (0.35)	14 (0.26)	23 (0.17)	4 (0.09)	37 (0.19)
Epistaxis	11 (0.39)	11 (0.21)	25 (0.18)	9 (0.21)	36 (0.19)
Rash NOS	6 (0.21)	14 (0.26)	17 (0.12)	9 (0.21)	31 (0.16)
Injection site bruising	0	15 (0.28)	16 (0.12)	0	31 (0.16)
Anxiety	8 (0.28)	16 (0.30)	13 (0.09)	3 (0.07)	29 (0.15)
Hypokalemia	15 (0.53)	8 (0.15)	20 (0.14)	12 (0.28)	28 (0.15)
Appetite decreased NOS	11 (0.39)	8 (0.15)	20 (0.14)	8 (0.19)	28 (0.15)
Insomnia	11 (0.39)	6 (0.11)	18 (0.13)	4 (0.09)	24 (0.13)
Rales	11 (0.39)	7 (0.13)	12 (0.09)	8 (0.19)	19 (0.10)
Cellulitis	10 (0.35)	5 (0.09)	13 (0.09)	4 (0.09)	18 (0.09)

[a] ≥ 20.0% frequency in any treatment group.

[b] Multiple reports of the same preferred term for a subject are only counted once within each treatment group.

[c] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

[d] Total exposure for azacitidine is the cumulative time from the first dose to the end of study (30 days after last dose), and for observation, is the cumulative time from randomization to withdrawal from study or day prior to crossover.

Sorted by decreasing frequency in the 8921/9221 all azacitidine group.

KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event

About twice as many subjects had at least 1 TEAE in the observation group as in azacitidine group in the 9221 trial. Subjects in 8421 and 8921 trials had more TEAEs than azacitidine subjects in 9221 trial.

In 9221 trial, some TEAEs were more frequent in the azacitidine group, and others in the observation group, reflecting the symptomatology of MDS and the subject population. The TEAEs more frequent in the azacitidine group were:

- Nausea, vomiting, constipation, anorexia
- Injection site erythema and bruising, pain
- Febrile neutropenia
- Dyspnea
- Erythema
- Arthralgia, pain in limb
- Pharyngitis

TEAEs more frequent in the observation group were:

- Anemia, thrombocytopenia
- Weakness
- Rash
- Anxiety
- Rales

3. First Occurrence of TEAEs by Cycle

As would be expected, some TEAEs occurred early in each cycle, during the administration of azacitidine, and declined later on during the cycle. Such events were nausea, vomiting, fever, diarrhea, constipation, fatigue, injection site erythema, bruising and pain, arthralgia, erythema, and insomnia.

Other events, such as anemia, leukopenia and thrombocytopenia, were most common during the middle of the cycle. In addition, some events persisted into the the last week of the cycle, such as fever, leukopenia, neutropenia, headache, anxiety, and weakness.

TEAEs were far more frequent in the first 2 cycles of treatment than in later cycles. This is graphically shown in sponsor's Table 20, shown below. For example, symptoms, such as nausea, vomiting, fever, diarrhea, constipation, injection site erythema and pain, and signs, such as anemia and thrombocytopenia, decreased by 50% to >90% between cycles 1-2 and subsequent cycles. There are a number of possible explanations for these findings: 1) the number of subjects decreased with increasing number of cycles, 2) the more severely affect subjects withdrew because of adverse events, 3) dose reductions in response to decreasing RBC, WBC and platelet counts and symptoms, 4) better preventive measures, 5) subjects' habituation to therapy, and 6) tolerance of medication.

Table 20: First Occurrence of TEAEs by Cycle Onset for the Most Frequently[a] Observed TEAEs in the 9221/9221 All Azacitidine Group

	Number (%) of Subjects					
	9221/9221 Subcutaneous					
	All Azacitidine[c] (N=239)					
Preferred Term[b]	Cycles 1-2 (N=220)	Cycles 3-4 (N=174)	Cycles 5-6 (N=116)	Cycles 7-12 (N=90)	Cycles 13-24 (N=41)	Cycle >24 (N=16)
At least 1 TEAE	218 (99.1)	150 (86.2)	80 (69.0)	82(91.1)	34 (82.9)	14 (87.5)
Nausea	113 (51.4)	14 (8.0)	7 (6.0)	6 (6.7)	1 (2.4)	0
Anemia NOS	130 (59.1)	9 (5.2)	3 (2.6)	3 (3.3)	1 (2.4)	2 (12.5)
Thrombocytopenia	125 (56.8)	7 (4.0)	3 (2.6)	3 (3.3)	1 (2.4)	0
Vomiting NOS	86 (39.1)	10 (5.7)	8 (6.9)	4 (4.4)	1 (2.4)	1 (6.3)
Pyrexia	58 (26.4)	21 (12.1)	8 (6.9)	8 (8.9)	6 (14.6)	4 (25.0)
Leukopenia NOS	80 (36.4)	18 (10.3)	4 (3.4)	2 (2.2)	1 (2.4)	0
Diarrhea NOS	41 (18.6)	14 (8.0)	6 (5.2)	8 (8.9)	0	2 (12.5)
Fatigue	46 (20.9)	8 (4.6)	8 (6.9)	3 (3.3)	3 (7.3)	1 (6.3)
Injection site erythema	56 (25.5)	9 (5.2)	3 (2.6)	2 (2.2)	2 (4.9)	1 (6.3)
Constipation	42 (19.1)	8 (5.2)	2 (1.7)	7 (7.8)	3 (7.3)	0
Neutropenia	52 (23.6)	10 (5.7)	3 (2.6)	2 (2.2)	2 (4.9)	1 (6.3)
Ecchymosis	34 (15.5)	13 (7.5)	6 (5.2)	3 (3.3)	3 (7.3)	5 (31.3)
Cough	31 (14.1)	10 (5.7)	4 (3.4)	9 (10.0)	2 (4.9)	1 (6.3)
Weakness	35 (15.9)	8 (4.6)	5 (4.3)	5 (5.6)	2 (4.9)	2 (12.5)
Dyspnea NOS	38 (17.3)	13 (7.5)	2 (1.7)	3 (3.3)	3 (7.3)	3 (18.8)
Edema	30 (13.6)	11 (6.3)	2 (1.7)	4 (4.4)	2 (4.9)	3 (18.8)
Petechiae	35 (15.9)	9 (5.2)	3 (2.6)	2 (2.2)	0	1 (6.3)
Injection site pain	29 (13.2)	12 (6.9)	3 (2.6)	2 (2.2)	0	0
Arthralgia	23 (10.5)	11 (6.3)	2 (1.7)	3 (3.3)	1 (2.4)	4 (25.0)
Headache NOS	25 (11.4)	6 (3.4)	4 (3.4)	6 (6.7)	2 (4.9)	2 (12.5)
Anorexia	22 (10.0)	7 (4.0)	2 (1.7)	2 (2.2)	0	3 (18.8)
Pharyngitis	19 (8.6)	5 (2.9)	2 (1.7)	9 (10.0)	3 (7.3)	1 (6.3)
Pain in limb	20 (9.1)	9 (5.2)	4 (3.4)	2 (2.2)	3 (7.3)	2 (12.5)
Edema peripheral	21 (9.5)	7 (4.0)	3 (2.6)	4 (4.4)	3 (7.3)	2 (12.5)
Dizziness	27 (12.3)	4 (2.3)	1 (0.9)	4 (4.4)	0	2 (12.5)
Contusion	13 (5.9)	8 (4.6)	3 (2.6)	5 (5.6)	2 (4.9)	4 (25.0)
Erythema	23 (10.5)	3 (1.7)	2 (1.7)	5 (5.6)	2 (4.9)	1 (6.3)
Epistaxis	19 (8.6)	5 (2.9)	1 (0.9)	3 (3.3)	1 (2.4)	1 (6.3)
Rash NOS	15 (6.8)	6 (3.4)	3 (2.6)	1 (1.1)	2 (4.9)	0
Injection site bruising	21 (9.5)	3 (1.7)	2 (1.7)	0	0	0
Anxiety	15 (6.8)	4 (2.3)	1 (0.9)	2 (2.2)	0	1 (6.3)
Hypokalemia	23 (10.5)	0	1 (0.9)	1 (1.1)	0	1 (6.3)
Appetite decreased NOS	15 (6.8)	6 (3.4)	2 (1.7)	1 (1.1)	2 (4.9)	0
Insomnia	12 (5.5)	4 (2.3)	0	1 (1.1)	0	0
Rales	12 (5.5)	4 (2.3)	1 (0.9)	1 (1.1)	0	1 (6.3)
Cellulitis	5 (2.3)	4 (2.3)	2 (1.7)	2 (2.2)	0	1 (6.3)

[a] ≥ 20.0% frequency in any treatment group

[b] Only the first occurrence of multiple reports of the same preferred term from a subject occurring after the first dose of azacitidine was counted

[c] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

Adverse events with missing start dates were excluded from counts by cycle.

KEY NOS=not otherwise specified, TEAE=treatment-emergent adverse event

Data Source: Table 15-48

4. Treatment-Related TEAEs:

The sponsor also tabulated adverse events as corrected by their occurrence in the observation group, and these are shown in sponsor's Table 23, shown below. The adverse event profile is very similar as in the previous tables, with gastrointestinal and hematologic adverse events being most prominent.

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Table 23: Most Frequently[a] Observed Treatment-Related TEAEs

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	9921	9221		9921/9221
Preferred Term[b]	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[c] (N=150)	Observation (N=92)	All Azacitidine[c] (N=220)
At least 1 treatment-related TEAE	48(100.0)	69 (97.1)	149 (99.3)	0 (0.0)	217 (98.6)
Nausea	26 (56.3)	55 (78.6)	94 (62.7)	0	149 (67.7)
Anemia NOS	36 (75.0)	41 (58.6)	92 (61.3)	0	133 (60.5)
Thrombocytopenia	34 (70.8)	38 (54.3)	93 (62.0)	0	131 (59.5)
Vomiting NOS	24 (50.0)	47 (67.1)	68 (44.0)	0	113 (51.4)
Leukopenia NOS	29 (60.4)	30 (42.9)	74 (49.3)	0	104 (47.3)
Injection site erythema	0	27 (38.6)	49 (32.7)	0	76 (34.5)
Pyrexia	17 (35.4)	26 (37.1)	46 (30.7)	0	72 (32.7)
Diarrhea NOS	18 (37.5)	23 (32.9)	49 (32.7)	0	72 (32.7)
Fatigue	9 (18.8)	16 (22.9)	50 (33.3)	0	66 (30.0)
Neutropenia	7 (14.6)	19 (27.1)	45 (30.0)	0	64 (29.1)
Injection site pain	0	13 (18.6)	35 (23.3)	0	48 (21.8)
Weakness	9 (18.8)	11 (15.7)	30 (20.0)	0	41 (18.6)
Constipation	10 (20.8)	5 (7.1)	33 (22.0)	0	38 (17.3)
Ecchymosis	11 (22.9)	9 (12.9)	27 (18.0)	0	36 (16.4)
Petechiae	16 (33.3)	14 (20.0)	22 (14.7)	0	36 (16.4)
Injection site bruising	0	14 (20.0)	16 (10.7)	0	30 (13.6)

[a] ≥ 20.0% frequency in any treatment group.
[b] Multiple reports of the same preferred term for a subject are only counted once within each treatment group
[c] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.
Sorted by decreasing frequency in the 8921/9221 all azacitidine group
KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event

5. Severity of Adverse Events

Non-serious adverse events were graded by CALGB Expanded Common Toxicity Criteria (CTC) and are shown in sponsor's Table 24 below. Grade 3 and 4 events in azacitidine-treated subjects were mainly hematologic (anemia, thrombocytopenia, neutropenia) as shown in sponsor's Table 26, while Grade 1 and 2 were mainly gastrointestinal. However, there were rare Grade 3 or 4 gastrointestinal and other events, as shown in Table 27.

Table 24: Nonserious TEAEs by Modified CALGB Expanded CTC Grade

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	9921	9221		9921/9221
CALGB CTC Grade	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[a] (N=150)	Observation (N=92)	All Azacitidine[a] (N=220)
At least 1 nonserious TEAE	48(100.0)	69 (98.6)	150(100.0)	69 (98.7)	219 (99.5)
Grade 1 (mild)	47 (97.9)	68 (97.1)	148 (98.7)	70 (85.9)	216 (98.2)
Grade 2 (moderate)	45 (93.8)	66 (94.3)	138 (92.0)	69 (75.0)	204 (92.7)
Grade 3 (severe)	43 (89.6)	53 (75.7)	129 (86.0)	66 (71.7)	182 (82.7)
Grade 4 (life-threatening)	37 (77.1)	47 (67.1)	87 (58.0)	32 (34.8)	134 (60.9)
Toxicity grade missing	14 (29.2)	14 (20.0)	42 (28.0)	16 (17.4)	56 (25.5)

[a] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.
KEY: CALGB=Cancer and Leukemia Group B, CTC=Common Toxicity Criteria, TEAE=treatment-emergent adverse event
Data Source: Table 15-14

Table 26: Most Frequently[a] Reported Nonserious CALGB CTC Grade 3 or 4 TEAEs in the Blood and Lymphatic System Disorders SOC

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Preferred Term[a]	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[b] (N=150)	Observation (N=92)	All Azacitidine[b] (N=220)
At least 1 CALGB toxicity grade 3 or 4 TEAE from the blood and lymphatic system SOC	42 (87.5)	60 (85.7)	134 (89.3)	64 (69.6)	194 (88.2)
Anemia NOS	32 (66.7)	37 (52.9)	87 (58.0)	40 (43.5)	124 (56.4)
Thrombocytopenia	30 (62.5)	35 (50.0)	83 (55.3)	28 (30.4)	118 (53.6)
Leukopenia NOS	24 (50.0)	20 (28.6)	56 (37.3)	11 (12.0)	76 (34.5)
Neutropenia	3 (6.3)	14 (20.0)	36 (24.0)	2 (2.2)	50 (22.7)

[a] ≥ 20.0% frequency in any treatment group.

[a] Multiple reports of the same preferred term for a subject are only counted once within each treatment group.

[b] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

Sorted by decreasing frequency in the 8921/9221 all azacitidine group.

KEY: CALGB=Cancer and Leukemia Group B, CTC=Common Toxicity Criteria, NOS=not otherwise specified, SOC=system organ class, TEAE=treatment-emergent adverse event

Data Source: Table 15-15

Table 27: Non-Hematologic Nonserious CALGB CTC Grade 3 or 4 TEAEs Occurring in ≥ 4.0% in Any Treatment Group

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Preferred Term[a]	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[b] (N=150)	Observation (N=92)	All Azacitidine[b] (N=220)
At least 1 CALGB toxicity grade 3 or 4 nonserious TEAE	45 (93.8)	64 (91.4)	139 (92.7)	75 (81.5)	203 (92.3)
Nausea	3 (6.3)	9 (12.9)	8 (5.3)	1 (1.1)	17 (7.7)
Fatigue	1 (2.1)	3 (4.3)	7 (4.7)	0	10 (4.5)
Dyspnea NOS	4 (8.3)	2 (2.9)	7 (4.7)	3 (3.3)	9 (4.1)
Weakness	3 (6.3)	4 (5.7)	4 (2.7)	4 (4.3)	8 (3.6)
Hyperglycemia NOS	2 (4.2)	3 (4.3)	3 (2.0)	4 (4.3)	6 (2.7)
Back pain	2 (4.2)	0	4 (2.7)	2 (2.2)	4 (1.8)
Dyspnea exertional	2 (4.2)	0	4 (2.7)	3 (3.3)	4 (1.8)
Pyrexia	2 (4.2)	0	3 (2.0)	1 (1.1)	3 (1.4)
Hypokalemia	2 (4.2)	0	1 (0.7)	4 (4.3)	1 (0.5)
Ecchymosis	2 (4.2)	1 (1.4)	0	0	1 (0.5)
Petechiae	2 (4.2)	0	0	0	0

[a] Multiple reports of the same preferred term for a subject are only counted once within each treatment group.

[b] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

Sorted by decreasing frequency in the 8921/9221 all azacitidine group.

KEY: CALGB=Cancer and Leukemia Group B, CTC=Common Toxicity Criteria, NOS=not otherwise specified, TEAE=treatment-emergent adverse event

Data Source: Table 15-15

Incidence of TEAEs by MDS subtypes did not show any trends and will not be shown.

6. Serious TEAEs, Deaths, Drug Discontinuations and Use of Concomitant Medications to Treat TEAEs

Serious TEAEs (SAEs) were more frequent in all azacitidine-treated patients (62%, range in the 3 studies was 61% - 71%) than in observation patients (37%). The most common in azacitidine-treated patients as compared to observation patients were:

- febrile neutropenia (in 12.7% vs. 3.3%)
- thrombocytopenia (in 7.3% vs. 2.2%)
- fever (in 11.8% vs. 2.2%), and
- pneumonia (in6.4% vs. 3.3%).

Most deaths occurred after withdrawal from study rather than during the study, as shown in sponsor's Table 30.

Table 30: Summary of Deaths

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Time of Death	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[a] (N=150)	Observation without crossover (N=41)	All Azacitidine[a] (N=220)
During study[b]	9 (18.8)	7 (10.0)	13 (8.7)	6 (14.6)	20 (9.1)
Following study withdrawal[c]	34 (70.8)	61 (87.1)	129 (86.0)	33 (80.5)	190 (86.4)
Total	43 (89.6)	68 (97.1)	142 (94.7)	39 (95.1)	210 (95.5)

[a] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation
[b] Death occurred within 30 days of last dose of azacitidine, or on or before the date of withdrawal in 9221 observation only subjects.
[c] Death occurred > 30 days after last dose of azacitidine, or after the date of withdrawal in 9221 observation only subjects.

The causes of death for the 35 subjects who died during the 3 CALGB studies are shown in sponsor's Table 31.

Table 31: Causes of Death in Subjects Who Died During the Study[a]

Study	Treatment	Subject	Cause(s) of Death (Investigator Verbatim Description)
8421	Azacitidine	38659	Respiratory failure
		38444	Generalized bleeding secondary to MDS
		37420	Multiple complications including myocardial infarction
		37421	Intracerebral hemorrhage
		37656	Fungal sepsis and cerebrovascular accident
		38232	Intracranial hemorrhage
		38345	Cardiopulmonary arrest
		38463	Small cell lung cancer
		38675	Pancytopenia/sepsis
8921	Azacitidine	44213	Intracranial hemorrhage
		44444	Marrow failure
		44726	Sepsis (Klebsiella)
		44902	Pneumonia
		45230	Bilateral lymphocytic interstitial pneumonitis with interstitial fibrosis
		45653	AML
		45746	Pneumonia[b]
9221	Observation without crossover	56168	Atherosclerotic heart disease
		57914	Congestive heart failure; respiratory failure
		59634	Dehydration/inanition
		60266	Respiratory failure
		61215	Subdural hematoma
		62440	Pneumonia; sepsis
	All azacitidine	55742	Necrotizing colitis
		56020	Respiratory failure
		56718	Bleeding/hemorrhage/central nervous system
		56741	Pneumonia
		57046	Cardiopulmonary arrest
		57311	Probable infection, progressive MDS
		57763	Bone marrow failure and acute leukemia
		59055	Intracranial hemorrhage
		59487	Cardiac arrest
		60256	MDS
		60431	Cardiopulmonary arrest
		60942	Infection
		61418	Coronary artery disease

[a] Death occurred within 30 days of last dose of azacitidine, or on or before the date of withdrawal in 9221 observation only subjects.

[b] Cause of death per Subject Completion page stated "not known"; however, pneumonia was reported as SAE with seriousness criterion of "death".

KEY MDS=myelodysplastic syndromes, AML=acute myelogenous leukemia, SAE=serious adverse event

In Study 8421 three subjects died as a result of CNS or generalized bleeding; all had low platelet counts at baseline requiring multiple platelet transfusions. Deaths occurred in two subjects after 1 cycle and in one, after 9 cycles. Two subjects died as a result of infections; both had been pancytopenic; both received 1 or 2 cycles of treatment. The remaining subjects died of a variety of causes after receiving 1 to 3 cycles of treatment. None of the deaths appeared to be treatment-related.

In Study 8921 four subjects died as a result of infections after treatment for 2 to 7 cycles. All had been pancytopenic and had low ANC at baseline that remained low throughout the study. One subject died from intracranial hemorrhage after 1 cycle of treatment. This subject had thrombocytopenia at baseline that became more pronounced with treatment and required multiple platelet transfusions. The remaining 2 subjects died of progression of MDS (marrow failure and AML). None of the deaths appeared to be treatment-related.

In Study 9221 observation group, one patient died of a subdural hematoma and one of infection. The other deaths do not appear to be MDS-related. In Study 9221 azacitidine group, infections were listed as causes of death in 3 subjects and intracranial hemorrhages in 2. It is possible that azacitidine may have contributed to infections or hemorrhages, which are part of the natural history of MDS.

During the follow-up period, 181/191 subjects in Study 9221 died (see Efficacy section, Secondary endpoint: Time To Death From Any Cause). About 64% of subjects died of MDS, AML, Sepsis, Other Infections, and Hemorrhages; about

25% died of other causes, mainly cardiac; causes of death were unknown in 11% (Listing 16.2.8.7.1A).

Other SAEs are shown in sponsor's Table 32.

Table 32: Serious TEAEs by Seriousness Criterion (Excluding Death)

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Seriousness Criterion[a]	Azacitidine (N=48)	Azacitidine (N=79)	All Azacitidine[b] (N=160)	Observation (N=82)	All Azacitidine[b] (N=220)
At least 1 SAE	33 (68.8)	42 (60.0)	89 (59.3)	33 (35.9)	131 (59.5)
Life-threatening	10 (20.8)	4 (5.7)	10 (6.7)	4 (4.3)	14 (6.4)
Hospitalization	29 (60.4)	41 (58.6)	82 (54.7)	31 (33.7)	123 (55.9)
Disabling/ incapacitating	0	0	2 (1.3)	0	2 (0.9)
Congenital anomaly	0	0	0	0	0
Medically important[c]	1 (2.1)	3 (4.3)	6 (4.0)	2 (2.2)	9 (4.1)

[a] Multiple reports of the same seriousness criteria from a subject were only counted once within each treatment group

[b] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

[c] Includes overdose and development of cancer, which were former serious adverse event criteria (see Section 4.1.2.2)

KEY: SAE=serious adverse event, TEAE=treatment-emergent adverse event

The most common life-threatening TEAEs in all studies were thrombocytopenia and anemia (n=4 each), respiratory failure (n=2), AML (n=2), dyspnea at rest and exertional (n=2 each). The other life-threatening TEAEs were reported in one subject each (bone marrow suppression, leukopenia, neutropenia, febrile neutropenia, cardiac failure congestive, abdominal pain, gastrointestinal obstruction, necrotizing colitis, chest pain, systemic inflammatory response syndrome, anaphylactic reaction, anaphylactic shock, sepsis, blood in stool, cachexia, dehydration, cerebral hemorrhage, convulsions, neurological symptoms, syncope, renal failure, and respiratory arrest).

The most common TEAEs that resulted in or prolonged hospitalizations were febrile neutropenia, thrombocytopenia, fever, and infections.

Azacitidine was discontinued in 18% of patients in Study 9221, in 29% of patients in Study 8921, and in 31% of patients in Study 8421. The most common reasons in Study 9221 were leukopenia (5%), neutropenia (3.6%), thrombocytopenia (3.6%), anemia (1.8%), and nausea, injection site pain, malaise, weakness, and pneumonia (0.9% each). Azacitidine dose was reduced in about 10% of patients, because of leukopenia, neutropenia and thrombocytopenia. Therapy interruption (dose held) occurred in about 21% of patients in Study 9221, in 17% of patients in Study 8921 and in 15% of patients in Study 8421. The main reasons cited for therapy interruption were leukopenia, neutropenia, and febrile neutropenia; the others were fever, nausea, vomiting, and thrombocytopenia.

PRBC and platelet transfusions were administered to about 76% of azacitidine patients and to 65% of observation patients. The main reasons were anemia (58%), thrombocytopenia (35%), fatigue (11%), epistaxis (3%) and patechiae (2%).

Concomitant medications to treat TEAEs were administered to almost all (95%) of azacitidine-treated patients and to 73% of observation patients. The symptoms requiring treatment are shown in sponsor's Table 40.

Table 40: Most Frequently[a] Observed TEAEs Treated With Concomitant Medication(s)

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
Preferred Term[b]	Azacitidine (N=48)	Azacitidine (N=70)	All Azacitidine[c] (N=150)	Observation (N=92)	All Azacitidine[c] (N=220)
At least 1 TEAE treated with concomitant medication(s)	45 (93.8)	67 (95.7)	142 (94.7)	67 (72.8)	209 (95.0)
Nausea	27 (56.3)	46 (65.7)	78 (52.0)	13 (14.1)	124 (56.4)
Vomiting NOS	17 (35.4)	40 (57.1)	56 (37.3)	4 (4.3)	97 (44.1)
Pyrexia	22 (45.8)	21 (30.0)	53 (35.3)	22 (23.9)	74 (33.6)
Constipation	14 (29.2)	12 (17.1)	40 (26.7)	5 (5.4)	52 (23.6)
Diarrhea NOS	13 (27.1)	9 (12.9)	20 (13.3)	5 (5.4)	29 (13.2)
Hypokalemia	13 (27.1)	8 (11.4)	19 (12.7)	12 (13.0)	27 (12.3)

[a] ≥ 20% in Any Treatment Group
[b] Multiple reports of the same preferred term for a subject were only counted once within each treatment group
[c] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation
KEY NOS=not otherwise specified, TEAE=treatment-emergent adverse event

Azacitidine-treated patients required more concomitant medications than observation patients, except for correction of hypokalemia (suggesting that hypokalemia may not have been treatment-related).

7. Laboratory Abnormalities

Hematology: As expected, mean values for RBCs, Hgb, WBC, ANC and platelet counts were all low at baseline. These values increased in patients who showed a response (CR or PR) or improvement resulting from treatment with azacitidine. Nadir analyses showed that RBC and platelet values tended to reach nadir values during the 3rd week of the cycle, while WBC and ANC values tended to reach nadir during the 2nd or 3rd week of the cycle. Mean time to nadir for RBC, WBC, ANC, and platelets was 15-16 days. Approximately 75% of the subjects reached the nadir values for most hematology parameters by the 3rd week of the cycle, indicating that the 28-day cycle generally allows sufficient time for subjects to reach cell count nadir, for WBC recovery and for dose adjustment prior to the next cycle.

Liver Function: Mean and median values for ALT, AST, LDH and total bilirubin generally remained unchanged throughout the first 12 cycles of azacitidine therapy. (The study entry inclusion criteria in this study specified 3-4 x ULN for liver enzymes rather than <2 x ULN for the SC studies).

Table 12.4-4: Mean and Median Data for Liver Chemistries Using Expanded Baseline Definition (By Month)

Laboratory Parameter (units) Time Point	Observation (N=92)			Azacitidine Only (N=99)			Azacitidine After Observation (N=51)			All Azacitidine (N=150)		
	N	Mean	Median	N	Mean	Median	N	Mean	Median	N	Mean	Median
ALT (U/L)												
Baseline	78	25 3	19.0	86	29 3	24 0	---	---	---	86	29 3	24 0
6 months	11	24 2	17.0	42	33 0	22 0	19	24.2	20.5	61	30 3	22 0
12 months	2	30 5	30 5	27	34 6	22.0	7	28 7	21 8	34	33 4	21 9
AST (U/L)												
Baseline	85	28.1	23.0	93	26 1	22 0	---	---	---	93	26 1	22 0
6 months	10	20 4	17.5	48	29.7	23.0	21	24.8	20.0	69	28 2	23 0
12 months	2	32 3	32.3	30	26 5	21 8	10	23 1	17 8	40	25 6	21 3
Alk Phos (U/L)												
Baseline	78	88 4	80 5	91	88 3	80 0	---	---	---	91	88 3	80 0
6 months	10	87 0	72.5	50	102 7	76 5	21	91 2	89 0	71	99 3	81 0
12 months	2	157.8	157 8	31	107 5	85 3	11	87 8	87 0	42	102 3	86 1
Total Bili (µmol/L)												
Baseline	86	14 9	12 1	92	14 4	12 0	---	---	---	92	14 4	12 0
6 months	11	17 0	13 7	50	14 9	13 7	22	11.9	11 0	72	14 0	12 6
12 months	2	10 1	10.1	31	13 5	12 0	11	12.3	12.0	42	13 2	12 0

KEY. ALT=alanine aminotransferase, AST=aspartate aminotransferase, Alk Phos=alkaline phosphatase, Total bili=total bilirubin

Table 61: Most Frequent[a] Hepatic TEAEs

SOC Preferred Term[b]	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	8421	8921	9221		8921/9221
	Azacitidine (N=45)	Azacitidine (N=75)	All Azacitidine[c] (N=150)	Observation (N=92)	All Azacitidine[c] (N=220)
At least 1 hepatic TEAE	15 (33.3)	8 (11.4)	18 (12.0)	7 (7.6)	26 (11.8)
Hepatobiliary Disorders	14 (28.2)	7 (10.0)	16 (10.7)	5 (5.5)	23 (10.5)
Jaundice NOS	5 (10.4)	3 (4.3)	5 (3.3)	2 (2.2)	8 (3.6)
Hepatomegaly	4 (8.3)	2 (2.9)	4 (2.7)	2 (2.2)	6 (2.7)
Cholelithiasis	0	1 (1.4)	3 (2.0)	3 (3.3)	4 (1.8)
Hepatosplenomegaly NOS	3 (6.3)	1 (1.4)	3 (2.0)	0	4 (1.8)
Hepatic failure	1 (2.1)	1 (1.4)	1 (0.7)	0	2 (0.9)
Hyperbilirubinemia	1 (2.1)	1 (1.4)	1 (0.7)	0	2 (0.9)
Hepatitis NOS	2 (4.2)	1 (1.4)	0	0	1 (0.5)
Investigations	3 (6.3)	3 (4.3)	2 (1.3)	1 (1.1)	5 (2.3)
Blood bilirubin increased	1 (2.1)	2 (2.9)	1 (0.7)	1 (1.1)	3 (1.4)
Liver function tests NOS abnormal	2 (4.2)	0	2 (1.3)	0	2 (0.9)

[a] ≥ 2.0% frequency in any treatment group
[b] Multiple reports of the same preferred term for a subject are only counted once within each treatment group
[c] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation
Sorted by descending frequency in the 8921/9221 all azacitidine group
KEY: NOS=not otherwise specified, SOC=system organ class, TEAE=treatment-emergent adverse event

The greatest percent of shifts to CTC grade 3 or 4 was observed for total bilirubin. These increases coincided with intercurrent illnesses, such as pneumonia, CHF, pulmonary edema, epigastric pain, gall stones, sepsis, viral hepatitis and transfusion reactions.

The overall frequency of subjects with at least 1 hepatic TEAE was 12.0% in the 9221 all azacitidine group, 7.6% in the 9221 observation group, 11.4% in the 8921 SC azacitidine group, and 33.3% in the 8421 IV azacitidine group (sponsor's Table

61, shown above). The most frequent hepatic TEAEs in studies 8921 and 9221 were jaundice, hepatomegaly, hepatosplenomegaly and cholelithiasis.

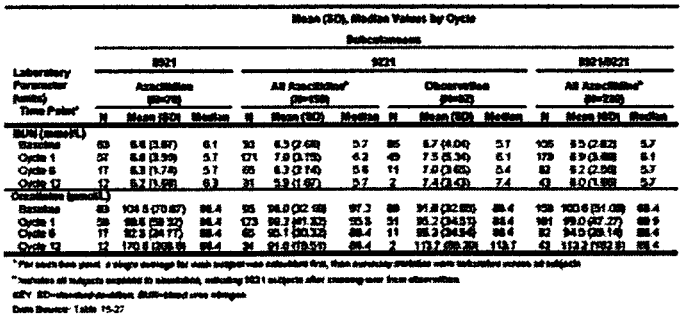
Three patients in the azacitidine-treatment arms developed hepatic failure. One patient had a long history of alcohol abuse. One patient had a long history of fatty liver and non-alcoholic cirrhosis; the increases in AST/ALT and total bilirubin in this patient resolved without changes in azacitidine treatment. The third patient with hepatic failure was not noted to have a history of hepatic insufficiency.

Most of the other TEAEs were related to the biliary system, such as biliary colic, cholangitis, cholelithiasis, and cholestatic jaundice.

Reviewer's Comments: Patients with hepatic impairment were excluded from the study. Most of the patients did not develop liver toxicity during treatment with azacitidine. However, some patients with histories of hepatic impairment experienced worsening of hepatic impairment. While the sponsor notes that no hepatic TEAEs resulted in dose reduction or discontinuation of treatment, the three patients with hepatic failure withdrew from the study.

Renal Function: The majority of subjects in all 3 studies had normal BUN and creatinine values at baseline and they remained normal at Cycles 1, 6, and 12.

Table 62: Mean and Median Data for Renal Function Chemistries (by Cycle)



Fewer than 10% of subjects in Studies 8921 and 9221 (all azacitidine group) had increases of BUN to grade 3 CTC. There was one patient in the 9221 study who developed renal failure, which led to therapy interruption. The subject later died of MDS. No other renal TEAEs (most frequent of which were dysuria, hematuria, renal impairment and urinary frequency) resulted in therapy interruption, dose reduction or discontinuation of treatment in the 3 studies. Renal function TEAEs were attributed to concomitant conditions and not to azacitidine treatment (sponsor's Table 65, shown below).

- No dose trends were seen with fever, leukopenia, neutropenia, rigors, patechiae, headache, anorexia, pharyngitis, pain in limb, peripheral edema, dizziness, contusion, insomnia and cellulitis.

9. Adverse Event - Gender Relationship

Sponsor's Table 72, shown below, lists TEAEs that occurred with a >10% difference in frequency between male and female study subjects. Female subjects were more likely than male subjects to experience vomiting, diarrhea, headache, arthralgias, erythema, injection site bruising, tachycardia and post-procedural hemorrhage. Male subjects reported thrombocytopenia more frequently than female subjects.

Table 72: TEAEs With a > 10.0% Difference in Frequency Between Males and Females (8921/9221 All Azacitidine Group) Without a Similar Trend in the 9221 Observation Group

	Number (%) of Subjects			
	Subcutaneous			
	9221 Observation (N=92)		8921/9221 All Azacitidine[b] (N=220)	
Preferred Term[a]	Male (N=60)	Female (N=32)	Male (N=150)	Female (N=70)
At least 1 TEAE	58 (96 7)	31 (96 9)	149 (99.3)	70 (100 0)
Vomiting NOS	5 (8.3)	0	73 (48.7)	46 (65.7)
Thrombocytopenia	28 (46.7)	14 (43.8)	104 (69.3)	40 (57.1)
Diarrhea NOS	10 (16.7)	3 (9.4)	47 (31.3)	33 (47.1)
Headache NOS	5 (8.3)	5 (15.6)	25 (16.7)	23 (32.9)
Arthralgia	2 (3 3)	1 (3.1)	28 (18.7)	21 (30.0)
Erythema	4 (6.7)	0	19 (12.7)	18 (25.7)
Injection site bruising	0	0	14 (9.3)	17 (24.3)
Tachycardia NOS	5 (8.3)	1 (3.1)	8 (5.3)	11 (15.7)
Post procedural hemorrhage	0	1 (3.1)	4 (2.7)	9 (12.9)

[a] Multiple reports of the same preferred term for a subject are only counted once within each treatment group.
[b] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.
Sorted by decreasing frequency in the 8921/9221 all azacitidine female group.
KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event

10. Adverse Event - Age Group Relationship

Sponsor's Table 73 lists adverse events that occurred with a >10% difference between age groups in both the azacitidine-treatment groups and in the CALGB 9221 observation group, which consisted of observation only subjects and observation before crossover subjects. The observation only group show little effect of age on the frequency of subjects reporting adverse events. Neutropenia was reported more frequently in subjects over 65 years of age than in younger subjects. Other adverse events were reported more frequently by younger patients. Treatment-related adverse events appear not to be age-related.

Table 69: Most Frequent* Renal TEAEs

	Number (%) of Subjects				
	Intravenous	Subcutaneous			
	9421	9921	9221		9921/9221
SOC Preferred Term[b]	Azacitidine (N=48)	Azacitidine (N=75)	All Azacitidine[c] (N=100)	Observation (N=92)	All Azacitidine[c] (N=220)
At least 1 renal TEAE	22 (45.8)	17 (24.3)	39 (39.3)	11 (12.0)	55 (25.0)
Renal and Urinary Disorders	22 (45.8)	16 (22.9)	37 (34.7)	11 (12.0)	53 (24.1)
Dysuria	3 (6.3)	4 (5.7)	14 (9.3)	2 (2.2)	18 (8.2)
Hematuria	3 (6.3)	0	7 (4.7)	3 (3.3)	7 (3.2)
Renal impairment NOS	4 (8.3)	3 (4.3)	4 (2.7)	1 (1.1)	7 (3.2)
Urinary frequency	5 (10.4)	4 (5.7)	3 (2.0)	1 (1.1)	7 (3.2)
Loin pain	0	0	6 (4.0)	1 (1.1)	6 (2.7)
Difficulty in micturition	0	0	4 (2.7)	1 (1.1)	4 (1.8)
Incontinence NOS	2 (4.2)	0	4 (2.7)	1 (1.1)	4 (1.8)
Nocturia	2 (4.2)	1 (1.4)	3 (2.0)	0	4 (1.8)
Renal failure NOS	2 (4.2)	0	3 (2.0)	1 (1.1)	3 (1.4)
Urinary hesitation	0	0	3 (2.0)	0	3 (1.4)
Cystocele	1 (2.1)	1 (1.4)	1 (0.7)	0	2 (0.9)
Micturition urgency	2 (4.2)	0	2 (1.3)	0	2 (0.9)
Urinary retention	1 (2.1)	0	2 (1.3)	0	2 (0.9)
Urine abnormal NOS	1 (2.1)	1 (1.4)	1 (0.7)	0	2 (0.9)
Renal cyst NOS	1 (2.1)	0	1 (0.7)	0	1 (0.5)
Anuria	1 (2.1)	0	0	0	0
Oliguria	2 (4.2)	0	0	0	0
Polyuria	1 (2.1)	0	0	1 (1.1)	0
Pyuria	1 (2.1)	0	0	0	0
Renal insufficiency	1 (2.1)	0	0	0	0
Stress incontinence	1 (2.1)	0	0	0	0
Investigations	1 (2.1)	2 (2.9)	4 (2.7)	0	6 (2.7)
Blood urea increased	1 (2.1)	2 (2.9)	3 (2.0)	0	5 (2.3)
Blood creatinine increased	1 (2.1)	1 (1.4)	3 (2.0)	0	4 (1.8)

[a] ≥ 2.0% frequency in any treatment group
[b] Multiple reports of the same preferred term for a subject are only counted once within each treatment group.
[c] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation
Sorted by decreasing frequency in the 9921/9221 all azacitidine group
KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event, SOC=system organ class
Data Source: Table 15.35

Reviewer's Note: Eligibility criteria for CALGB trials included serum creatinine ≤1.5 x normal and serum CO_2≥19 mEq/L. There were no differences in the incidence of TEAEs in patients with normal creatinine clearance and in patients with creatinine clearance elevated to 1.5 x normal (Table 12.2-10, CALGB Study 9221, not shown). The mean and median values of BUN and creatinine did not change during 12 cycles of treatment, suggesting that azacitidine did not adversely affect renal function in most patients. There were 2 patients who developed renal failure in study 8421, none in study 8921, 3 in the azacitidine-treated patients in study 9221, and 1 in the observation arm of study 9221. There were concomitant medical conditions and events such as sepsis, hypotension, previous history of renal insufficiency, hypertension, and diabetes mellitus. Individual case histories do not suggest azacitidine causing renal toxicity.

8. Adverse Event-Dose Relationship

Analysis of TEAEs by dose (Table 66, ISS) led to the following conclusions:

- Gastrointestinal events, i.e. nausea, vomiting, diarrhea and constipation, tended to increase with increasing doses of azacitidine. For example, nausea occurred in 63% of patients receiving ≥100 mg/m^2, in 54% receiving ≥75 mg/m^2, and in 34% receiving >75 mg/m^2 azacitidine.
- Other events appeared to increase with increasing doses of azacitidine, such as anemia, injection site erythema, ecchymosis, weakness, dyspnea, site pain and arthralgia. However, the trends were less clear than in the case of gastrointestinal events.
- No clear dose-related trends were seen with cough, erythema, epistaxis, rash, injection site bruising, anxiety, hypokalemia and rales.

Table 73: TEAEs With a > 10.0% Difference in Frequency Across Age Groups (8921/9221 All Azacitidine Group) Without a Similar Trend in the 9221 Observation Group

	Number (%) of Subjects					
	Subcutaneous					
	9221 Observation (N=92)			8921/9221 All Azacitidine[b] (N=220)		
Preferred Term[a]	<65 Years (N=33)	≥65 Years (N=58)	≥75 Years (N=25)	<65 Years (N=79)	≥65 Years (N=137)	≥75 Years (N=52)
At least 1 TEAE	33 (100.0)	56 (96.6)	23 (92.0)	79 (100.0)	137 (100.0)	52 (100.0)
Neutropenia	4 (12.1)	6 (10.3)	3 (12.0)	20 (25.3)	50 (36.5)	19 (36.5)
Injection site erythema	0	0	0	33 (41.8)	43 (31.4)	13 (25.0)
Pharyngitis	3 (9.1)	4 (6.9)	1 (4.0)	22 (27.8)	22 (16.1)	10 (19.2)
Injection site pain	0	0	0	20 (25.3)	29 (21.2)	7 (13.5)
Night sweats	1 (3.0)	2 (3.4)	1 (4.0)	12 (15.2)	7 (5.1)	3 (5.8)
Hematoma NOS	0	0	0	11 (13.9)	8 (5.8)	2 (3.8)

[a] [illegible]

[b] Includes all subjects exposed to azacitidine, including 9221 subjects after crossing over from observation.

Sorted by decreasing frequency in the 8921/9221 all azacitidine ≥ 75 years age group.

KEY: NOS=not otherwise specified, TEAE=treatment-emergent adverse event

11. Adverse Events from Published Literature and Other Sources

The sponsor performed a search for safety information in the following electronic databases: Medline, Embase, Biosis, Derwent Drug File, and ADIS Clinical Trials. The publications describe the clinical use of azacitidine in more than 2000 subjects over a 30-year period. In these studies, azacitidine was given orally in encapsulated form, IV by rapid bolus injection, IV by continuous infusion, and by SC injection. The doses ranged from single-dose of 25 mg/m^2 IV to 750 mg/m^2 IV for 10 days.

In addition to the 3 CALGB trials, described in this NDA review, there were 7 other non-CALGB studies of azacitidine treatment in MDS (described in Background, above). These studies noted bone marrow suppression, gastrointestinal events (nausea, vomiting, and diarrhea), and injection site reactions. Hepatic toxicity or renal toxicity were not described. One subject experienced a severe serum sickness-like illness.

Of non-MDS safety studies, 5 were dose comparison or dose escalation studies, 1 evaluated hepatic effects of azacitidine, and 2 evaluated renal effects. The subjects in these studies had a variety of solid tumors and acute leukemias. They were treated with a variety of azacitidine dosage regimens. Azacitidine was administered by IV bolus or infusion in 7 studies and SC in 1 study. These studies showed that

- MTD was about 150 mg/m^2 for 5 days every 2 weeks. The DLT events were severe nausea and vomiting, accompanied by weight loss. Hematological toxicity increased with increasing azacitidine dose. These toxicities were noted in all studies.
- Less hematological and gastrointestinal toxicity was observed when azacitidine courses were given very 21 to 28 days.

- In 36 children with AML or ALL refractory to standard treatment, the MTD was 150 to 200 mg/m^2/day. DLT were nausea, vomiting, diarrhea in all subjects who received ≥150 mg/m^2/day. Prolonged myelosuppression occurred at doses ≥200 mg/m^2/day.
- Effects of azacitidine on hepatic function were studied in 28 cancer patients with or without hepatic metastases. Abnormal LFTs (serum bilirubin and or SGOT >3 x ULN) occurred in 7/20 (35%) of subjects. Four patients with significant hepatic tumor burden prior to azacitidine therapy died of rapidly progressive hepatic coma. The authors concluded that azacitidine is potentially hepatotoxic in subjects with pre-existing liver disease.
- Effects of azacitidine on renal function were evaluated in 2 studies. In the first study, 22 subjects with acute leukemia were treated with doses of 100 to 200 mg/m^2/day for 5 or 7 days. Polyuria, glycosuria and/or transient changes in bicarbonate or phosphorus were detected during 29/33 courses of azacitidine in 20/22 subjects. Eleven subjects had a history of azotemia. All subjects received concomitant antineoplastic drugs and antibiotics. The authors concluded that these findings were suggestive of defective tubular function. In the second study, 11 subjects with acute leukemia were treated with azacitidine 150 mg/m2/day for 5 days. Hypophosphatemia occurred during 4/40 courses of azacitidine. Hypokalemia occurred during 2/30 courses of azacitidine in another group of 12 subjects. The authors concluded that these electrolyte changes were due to modest azacitidine-associated renal tubular toxicity. No additional studies were performed to support this conclusion.
- A comprehensive review of all the studies by Von Hoff described adverse events in over 800 subjects with a variety of neoplastic disorders who received doses ranging from 60 mg/m^2 to 750 mg/m^2 given once or in repeated doses up to 10 days. The adverse event profile in these studies is similar to that described in the studies described above and also in this NDA.
  - Hematologic effects. Myelosuppression was the major adverse effect. The granulocytic nadir occurred 14 to 17 days following administration, with a median duration of about 2 weeks. Both leukopenia and thrombocytopenia were dose-dependent. Anemia was rare.
  - Gastrointestinal effects. Nausea and vomiting were dose-limiting toxicities. MTD IV doses were 500 mg/m^2 when given weekly, and 150 to 200 mg/m^2/day for 5 days given every 14 to 28 days. Mild-to-moderate nausea and vomiting was generally controlled with antiemetics. Diarrhea occurred in about 50% of subjects, but was easily controlled.
  - Hepatic effects. Abnormal hepatic function changes attributable to azacitidine occurred in about 7% of patients. Hepatic coma was present in 0.5% of subjects. The hepatic effects did not appear to be related to dose, schedule, or route of administration of azacitidine. Von Hoff recommended cautious use in patients with underlying liver disease.
  - CNS effects. CNS toxicity has been reported but is infrequent with azacitidine therapy. Two of 8 subjects with disseminated neoplasms in a Phase I study evaluating azacitidine 150 mg/m^2 to 200 mg/m^2 given daily as a constant IV infusion over 5 days every 28 days developed

somnolence, apathy, disorientation, and agitation. Both patients recovered a normal sensorium after discontinuation of treatment. Fifteen of 154 subjects treated with azacitidine with a variety of treatment schedules developed coma; however, only 2 did not have comorbid conditions that may have contributed to the event. Four had CNS leukemia, 3 had sepsis, and the others had intracranial hemorrhage, azotemia, stupor prior to azacitidine, and obtundation associated with hypotension.

- Muscle tenderness and weakness. One author reported an unusual syndrome of generalized muscle tenderness, weakness, and lethargy in 17 of 18 subjects with AML treated with IV azacitidine that began on Day 3 of a 5-day treatment and lasted for 7 to 10 days. No other author has described this syndrome.
- Renal effects. Renal abnormalities ranging from elevated serum creatinine to renal dysfunction and death were reported rarely in subjects treated with IV azacitidine in combination with other chemotherapeutic agents.
- Death. Six of 745 subjects died from drug related causes, hepatic coma in three, thrombocytopenia in two, and hypotension in one.

NCI annual reports to the FDA document that during the years 1975 through 2002 approximately 7400 subjects had been treated with azacitidine for a variety of neoplastic diseases and various hemoglobinopathies.

- A total of 87 deaths were reported and azacitidine was identified as a possible orprable contributor to 21 of the deaths. The most common causes of deaths were infections, thrombocytopenia and neutropenia. Other causes were ARDS, hepatotoxicity and diffuse pulmonary hemorrhage.
- The most common SAEs, besides deaths, were myelosuppression, infectious complications, nausea/vomiting, and hepatotoxicity (5 subjects).
- Other significant adverse events included elevated LFTs, renal failure, and neurological events (confusion, stupor, seizure, and ataxia).

D. Adequacy of Safety Testing

Safety testing was carefully performed during the CALGB trials. The sponsor collected the data retrospectively, and was successful in compiling virtually all adverse event and laboratory data as documented in Patient Profiles, tables and listings.

E. Summary of Critical Safety Findings and Limitations of Data

1. This NDA documents the safety profile of azacitidine in 226 subjects, 220 of them in the 3 clinical trials and 6 in a clinical pharmacology study. Additional information is available from published studies and unpublished safety reports. Azacitidine has been in clinical use for about 30 years. More than 7000 patients have been treated with this agent at various doses and in various regimens. This information is useful in corroborating the safety profile in this NDA and in alerting the reviewer to rare adverse events.

2. 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.
3. The same dose of azacitidine was used in the 3 clinical trials. The drug was administered SC in the randomized, controlled trial and in one uncontrolled supportive trial, and IV in the other uncontrolled supportive trial. The extent of exposure by dose was similar in 3 three trials. However, the total exposure, calculated by subject-years was the shortest in the IV azacitidine trial (a mean of 0.59 year per subject), intermediate in the SC azacitidine single-arm trial (a mean of 0.74 year per subject) and the longest in the randomized controlled trial (a mean of 0.92 per subject).
4. The most frequent reason for withdrawal from the trials was no response to azacitidine, followed by development of AML, adverse event, subject's choice to discontinue, other reasons, and death.
5. There were no deaths that were attributed to azacitidine toxicity in these trials. Of the 36 deaths during the 3 trials, 18 were probably related to MDS (7 were attributed to infections, 5 to bleeding, 4 to marrow failure, and 2 to AML). Other causes of death appear to be unrelated to MDS.
6. The serious adverse events occurred in about 60% of azacitidine-treated patients and in about 36% of observation only patients. About 56% of azacitidine-treated patients had adverse events that led to hospitalization, as compared to 34% of observation only patients. About 6% of azacitidine-treated patients had life-threatening adverse events, as compared to 4% of observation only patients. The most common SAEs that resulted in hospitalizations or that prolonged hospitalizations were thrombocytopenia, febrile neutropenia, fever and pneumonia.
7. About 30% of subjects experienced adverse events during 30 days prior to study entry. The most common were anemia (in 10%), thrombocytopenia (in 7%), fever (in 4%), neutropenia (in 3%), and diarrhea (in 3%). These adverse events were reported more frequently in subjects that were randomized to the observation only group (17% had anemia, 13% had thrombocytopenia, 9% had fever, 8% had neutropenia, and 4-5% had diarrhea, hypokalemia, rigors, anorexia and headache).
8. Virtually all subjects reported adverse events during the study, 99.5% in the azacitidine-treated groups in the 3 trials and 96.7% in the observation only group. A greater proportion of azacitidine-treated subjects reported the following adverse events as compared to observation only subjects: gastrointestinal events (nausea, vomiting, diarrhea, constipation, anorexia), hematologic (neutropenia, leukopenia, fever, rigors, ecchymoses, patechia, epistaxis), injection site (erythema, bruising and pain), cough, dyspnea, arthralgia, headache, weakness, dizziness and insomnia. After correction for the mean duration of exposure (2-fold longer in the azacitidine subjects), observation only subjects were found to have twice as many subjects with TEAEs than azacitidine subjects, including more subjects with anemia and thrombocytopenia. There were more subjects reporting nausea, vomiting and

constipation among azacitidine-treated subjects than among observation only subjects.

9. During treatment with azacitidine, some TEAEs occurred early in the cycle (nausea, vomiting, fever, diarrhea, constipation, injection site pain, arthralgia), others in the middle of the cycle (anemia, leukopenia and thrombocytopenia), and some persisted in the last week of the cycle (fever, leukopenia, neutropenia, headache, anxiety and weakness). Subjects reported the most TEAEs in the first 2 cycles of azacitidine therapy and progressively fewer in subsequent cycles.
10. The most common reasons for azacitidine discontinuation, dose reduction or therapy interruption were leukopenia, neutropenia, thrombocytopenia.
11. PRBC and platelet transfusions were administered to about 76% of azacitidine-treated patients and to 65% of observation only patients. The main reasons were anemia, thrombocytopenia, and fatigue.
12. Concomitant medications to treat adverse events were administered to almost all (95%) of azacitidine-treated patients and to 73% of observation only patients. The most common conditions treated in the azacitidine treatment subjects were nausea, vomiting, fever, constipation, diarrhea and hypokalemia. The most common conditions treated in the observation only group were fever, hypokalemia and nausea.
13. Blood cell counts were low at baseline in all subjects and decreased in subjects treated with azacitidine. Blood counts increased in subjects who showed a response or improvement.
14. Liver function TEAEs occurred in about 16% of azacitidine-treatment groups and in about 8% in observation only group. In most cases, liver function TEAEs coincided with intercurrent illnesses, including hepatobiliary disorders, and were not attributed to azacitidine treatment. Three patients developed hepatic insufficiency during azacitidine treatment; two of them had prior histories of liver cirrhosis.
15. Renal TEAEs were rare, transient and attributed to concomitant conditions and events, not to azacitidine treatment. Five patients in the azacitidine treatment groups and one patient in observation only group developed renal failure.
16. Gastrointestinal TEAEs tended to increase with increasing dose of azacitidine. Other events were less dose-related, such as anemia, erythema, ecchymosis, weakness, dyspnea, site pain and arthralgia. Most types of TEAEs were unrelated to dose.
17. Some treatment-related adverse events were more frequent in females than in males. These included vomiting, diarrhea, headache, injection site erythema, arthralgia, tachycardia, and post-procedural hemorrhage.
18. Treatment-related adverse events were not more frequent in older subjects.
19. Gastrointestinal and hematologic TEAEs were reported in all published studies, and were dose-limiting. The authors of one study concluded that azacitidine is potentially hepatotoxic in subjects with pre-existing liver disease. Renal function abnormalities were reported in two studies, but not others. CNS toxicity was reported as infrequent, mostly in the presence of comorbid conditions. One author reported a syndrome of muscle tenderness, lethargy and weakness in

AML patients treated with azacitidine. Death was thought to be drug-related in 6 of 745 azacitidine-treated subjects (due to hepatic coma in three, thrombocytopenia in two, and hypotension in one). Azacitidine was identified as a possible or probable contributor to 21 deaths in cancer patients reported by NCI. Most of deaths were due to infections, neutropenia, and thrombocytopenia.

20. Even though azacitidine had been administered to a very large number of patients, the trials in this NDA have enrolled the largest number of patients with any one condition. All the other trials and reports described smaller number of patients. Thus, the adverse event database is much smaller than the usage of the medication may indicate.
21. Another limitation of this safety evaluation is that the data have been re-collected by the sponsor from hospital records and not from the original CRFs.
22. Azacitidine appears to be a relatively safe drug for treatment of a malignant or pre-malignant condition such as MDS. Azacitidine-related adverse events appear to be relatively easily controlled with concomitant medications and blood product use.

VIII. Dosing, Regimen, and Administration Issues

The dosing regimen of 75 mg/m^2/day for 7 days every 28 days has been used in all 3 studies in 270 subjects and appears to be maximally effective and reasonably well tolerated, especially after 1-2 cycles of treatment. Dose adjustments according to hematologic parameters have been effective. Administration SC or IV is supported by results of 2 trials and one trial, respectively.

The issues are: 1) how long to administer azacitidine before stopping for failure to achieve response, and 2) how long to administer azacitidine after patients have achieved complete response.

According to protocol, subjects who failed to achieve a response after 4 cycles of therapy were to be taken off study. This directive proved to be unrealistic. Before a response was achieved, there was an "initial positive effect", defined as the first day of achievement of target for ≥4 weeks for at least one abnormality at baseline. In most subjects the "initial positive effect" consisted of a decrease in bone marrow blasts. In CALGB 9221 study, 18 subjects (82%) had the "initial positive effect" after 4 cycles, the remaining 4 the "initial positive effect" after 5, 6, 7 (a CR), and 17 cycles, respectively. In CALGB 8921 study, all 10 subjects had an "initial positive effect" within 2 cycles, and in CALGB 8421 study, all 9 responders had an "initial positive effect" with in 3 cycles. Full achievement of responses occurred considerably later after the "initial positive response". Thus, 36 of 41 (88%) subjects in the ITT population who achieved a response had an "initial positive effect" within 4 cycles of treatment. Azacitidine treatment should be administered for at least 4 weeks before it is stopped for lack of effectiveness. During this period there should occur an "initial positive response" presaging a response.

According to protocol, subjects who achieved a complete response (CR) were to have 3 additional cycles of therapy before therapy is discontinued. Three subjects with CR were continued on azacitidine until withdrawn from the study for other reasons. In CALGB 9221, the median number of therapy cycles received by the 22 responders was 13.5 (range, 7 to 89 cycles). In CALGB study 8921, the median number of cycles received by the 10 responders was 14.5 (range, 7 to 157 cycles). In CALGB study 8421, the median number of cycles received by 9 responders was 12 (range, 2 to 15 cycles). The median number of cycles of therapy received by all responders in the 3 trials was 13 cycles (range, 2 to 157 cycles). The sponsor's recommendation to continue azacitidine therapy in subjects with partial and complete responses for as long as patients continue to benefit is reasonable.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Analyses and Adequacy of Investigation

Reviewer's Table below summarizes the composite data for gender analysis for efficacy (CR + PR) in all 3 studies. There appear to be no gender differences in response rates.

Reviewer's Table. Gender Analysis for Efficacy (CR + PR), ITT Population

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%)

For safety analysis by gender, the sponsor analyzed the frequency of treatment-related adverse events in male and female subjects. 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.

B. Evaluation of Evidence of Age, Race, or Ethnicity Effects on Safety or Efficacy

Reviewer's Table below summarizes the data for response rates (CR + PR) by age groups in all 3 studies. There appear to be no age differences in response rates when the data from all 3 trials are assembled, even though there are wide differences in response rates between age groups within each trial.

Reviewer's Table. Response Rates (CR + PR) By Age Groups, ITT Population

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%)

The sponsor carried out a safety analysis by age groups of <65 years of age, ≥65 years of age, and ≥75 years of age. The frequencies of treatment related adverse events did not increase with age. Except for neutropenia, there was a higher frequency of some TEAEs (pharyngitis, injection site erythema and pain, nightsweats, and hematolma) in the <65 year-old group than in the >65 year-old group.

Analysis by race could not be carried out because 94.8% of subjects in the 3 studies were of the White race. Reviewer's Table below shows the racial demographics in the 3 studies.

Reviewer's Table. Racial Demographics in the Three CALGB Studies, ITT Population

Race	CALGB 9221	CALGB 8921	CALGB 8421	Total
White	140/150	68/72	48/48	256/270 (94.8%)
Black	2/150	2/72	0	4/270 (1.5%)
Hispanic	5/150	1/72	0	6/270 (2.2%)
Asian	3/150	1/72	0	4/270 (1.5%)

C. Evaluation of Pediatric Program

The sponsor is not proposing pediatric studies. Azacitidine was designated as an Orphan Drug on December 3, 2001 (designation request #01-1501).

D. Comments on Data Available or Needed in Other Populations

- As shown above, there is scanty data on the effect of azacitidine in MDS in other races other than White, although there is no reason to postulate response differences in other races.
- Patients with mild hepatic or renal impairment were excluded from the CALGB studies. Safety data on these patients can be obtained in the post-marketing period.

X. Conclusions and Recommendations

A. Conclusions

1. Azacitidine treatment resulted in reproducible responses in about 15% of subjects. The responses were long-lasting and resulted in clinical benefit, consisting of complete or partial normalization of peripheral blood counts and bone marrow blast percentages and of loss of transfusion-dependence. In

addition, approximately 17% of subjects had a clinical benefit termed Improvement, which consisted of increased blood counts and loss of transfusion dependence in transfusion-dependent subjects. The median duration of Improvement was 195 days. Observation only subjects had 0% responses or improvement. The difference in response rates between the azacitidine-treated subjects and observation only subjects was statistically significant ($p>0.0001$). There is at present no drug that shows similar efficacy in treatment of MDS.

2. All subtypes of MDS and also AML (initially diagnosed as MDS) had similar response rates. There were no differences in response rates between males and females, and between different age groups. Virtually all study subjects were of the White race; there is no information on response rates in other races or ethnic groups. Cytogenetic analyses were not carried out in these trials. Responders generally had tri-lineage deficits, but so did the majority of study subjects. Thus, there are no predictors of a response.
3. Increased survival resulting from azacitidine treatment, as compared to observation only, could not be demonstrated in the controlled trial. There are several reasons for this failure: 1) the randomized study was not powered to demonstrate a survival advantage, given the low response rate (15%), the unrealistic statistical plan in the protocol (30% response rate in the azacitidine arm and 10% in the observation arm), and the long median survivals in non-responders as well as in responders, 2) crossover of more than half of the observation only arm to azacitidine treatment, resulting in loss of matching of the randomized populations, and 3) the high median age of MDS patients, resulting in 40% of subjects dying from causes other than MDS, AML or complications of MDS during the study. A much larger study would be needed to show a survival advantage of azacitidine treatment.
4. Azacitidine dosing is well-established in these trials. Duration of treatment is less clear-cut. According to protocol, subjects were to discontinue treatment after 4 cycles if they did not have a response. However, among the responders, only the "initial positive effect" (most often a decrease in percentage of blasts) was evident by cycle 4 in 82% of subjects and by cycle 7 in 95% of subjects. The degree of response (complete or partial) became evident later. These findings suggest that treatment should be longer than 4 cycles before a patient is declared a non-responder. Partial responders were treated for the duration of response. Complete responders either discontinued treatment after achieving a complete response and receiving 3 more cycles of treatment, or continued treatment for duration of the response.
5. Azacitidine was a relatively safe drug in the 3 trials considering the malignant or pre-malignant nature of MDS. Serious adverse events were common and generally due to consequences of decreases in blood counts, already low in MDS. The most common adverse events were gastrointestinal. However, all adverse events decreased after the first two cycles of treatment, as gastrointestinal symptoms were controlled by concomitant medications and blood counts improved as a result of responses to azacitidine. There were no deaths ascribed solely to azacitidine.

6. In summary, azacitidine benefits a minority of patients with MDS but is relatively safe. The main benefit is loss of transfusion-dependence. These trials did not establish increased survival or reduction of risk to progression to AML. The main discomforts are long-term administration of SC medication and use of concomitant medications to control gastrointestinal side effects.
7. An adequately powered trial to demonstrate a survival benefit of azacitidine treatment is unlikely, given the relative rarity of qualifying subjects, the low response rate, and the great variability in survival of the mostly elderly subjects.
8. Approval of the drug is supported by the results of one controlled trial and two uncontrolled trials, all yielding consistent results.

B. Recommendations

1. Azacitidine should receive a regular approval for treatment of all types of MDS.
2. The goals of treatment should be defined in the drug label, such as correction of transfusion-dependence, hemorrhage, thrombocytopenia, neutropenia, symptomatic anemia, or increased bone marrow blasts.
3. Pharmacology data on the role of cytochrome P450 enzymes in azacitidine metabolism and the activity of azacitidine metabolites should be obtained in the post-marketing period.
4. Safety of azacitidine in patients with mild hepatic or renal impairment should be obtained in the post-marketing period.

XI. APPENDIX

1. List of Improvements in NDA 50-794 According to the Reviewer

CALGB 9221 Improvements: 19 in the originally randomized to Azacitidine, 11 in Crossover

Azacitidine	Azacitidine after Crossover
55914, 56424, 56562,56859, 57191, 57289, 57502, 58116, 59909, 60163, 60360, 60484, 60939, 61030, 61720, 61799, 62422, 62471, 62605	55980, 56190, 56571, 58163, 59057, 60302, 60983, 61225, 61261, 61418, 62280

CALGB 8921 Improvements: 6
Improvements: 44100, 44187, 45371, 45464, 45755, 46131.

CALGB 8421 Improvements: 8
Improvements: 37521, 38320, 38320, 37650, 38495, 38376, 39656, 38840.
Patient #38477 had PR, not Improvement.

2. List of No Improvements (Reviewer disagrees with sponsor's assessment)

Study 9221 subjects whom the sponsor listed as having an Improvement response and the reviewer thought had no Improvement (most of them had only a decrease in blasts, and no changes in blood cell counts or transfusions): 38

55973, 56366, 60266, 60638, 56250, 56504, 56531, 57182, 57663, 59422, 60205, 60445, 60708, 62377, 59050, 59055, 59397, 59585, 60111, 60438, 61019, 61489, 61656, 62131, 62007, 62377, 55973, 60266, 60638, 56250, 56504, 56531, 57182, 57663, 59422, 60205, 60445, 60708.

In Study 8421, the following 4 patients had no Improvement: 38345, 39947 had no PR and no Improvement, 36554, 36727.

In Study 8921, the following 5 patients had no Improvement: 39699, 44880, 45842, 46164, 46583.

3.Adverse Events Occurring in ≥5 % of Patients (from Sponsor's Proposed label)

Most Frequently Observed Adverse Events (≥ 5% in All Vidaza)*

Preferred Term**	All Vidaza‡ (N=220)	Observation† (N=92)
At least 1 TEAE	219 (99.5)	89 (96.7)
Nausea	155 (70.5)	16 (17.4)
Anemia	153 (69.5)	59 (64.1)
Thrombocytopenia	144 (65.5)	42 (45.7)
Vomiting	119 (54.1)	5 (5.4)
Pyrexia	114 (51.8)	28 (30.4)
Leukopenia	106 (48.2)	27 (29.3)
Diarrhea	80 (36.4)	13 (14.1)
Fatigue	79 (35.9)	23 (25.0)
Injection site erythema	77 (35.0)	0
Constipation	74 (33.6)	6 (6.5)
Neutropenia	71 (32.3)	10 (10.9)
Ecchymosis	67 (30.5)	14 (15.2)
Cough	65 (29.5)	14 (15.2)
Dyspnea	64 (29.1)	11 (12.0)
Weakness	64 (29.1)	19 (20.7)
Rigors	56 (25.5)	10 (10.9)
Petechiae	52 (23.6)	8 (8.7)
Injection site pain	50 (22.7)	0
Arthralgia	49 (22.3)	3 (3.3)
Headache	48 (21.8)	10 (10.9)
Anorexia	45 (20.5)	6 (6.5)
Pain in limb	44 (20.0)	5 (5.4)
Pharyngitis	44 (20.0)	7 (7.6)
Back pain	41 (18.6)	7 (7.6)
Contusion	41 (18.6)	9 (9.8)

Preferred Term**	All Vidaza‡ (N=220)	Observation† (N=92)
At least 1 TEAE	219 (99.5)	89 (96.7)
Dizziness	41 (18.6)	5 (5.4)
Edema peripheral	41 (18.6)	10 (10.9)
Erythema	37 (16.8)	4 (4.3)
Chest pain	36 (16.4)	5 (5.4)
Epistaxis	36 (16.4)	9 (9.8)
Febrile neutropenia	36 (16.4)	4 (4.3)
Myalgia	35 (15.9)	2 (2.2)
Weight decreased	35 (15.9)	10 (10.9)
Abdominal pain	34 (15.5)	12 (13.0)
Pallor	34 (15.5)	7 (7.6)
Nasopharyngitis	32 (14.5)	3 (3.3)
Pitting edema	32 (14.5)	9 (9.8)
Skin lesion	32 (14.5)	8 (8.7)
Dyspnea exertional	31 (14.1)	15 (16.3)
Injection site bruising	31 (14.1)	0
Rash	31 (14.1)	9 (9.8)
Injection site reaction	30 (13.6)	0
Anxiety	29 (13.2)	3 (3.3)
Appetite decreased	28 (12.7)	8 (8.7)
Fatigue aggravated	28 (12.7)	4 (4.3)
Hypokalemia	28 (12.7)	12 (13.0)
Upper respiratory tract infection	28 (12.7)	4 (4.3)
Pruritus	27 (12.3)	11 (12.0)
Abdominal tenderness	26 (11.8)	1 (1.1)
Depression	26 (11.8)	7 (7.6)
Productive cough	25 (11.4)	4 (4.3)
Insomnia	24 (10.9)	4 (4.3)
Malaise	24 (10.9)	1 (1.1)
Pain	24 (10.9)	3 (3.3)
Pneumonia	24 (10.9)	5 (5.4)
Abdominal pain upper	23 (10.5)	3 (3.3)
Crackles lung	23 (10.5)	8 (8.7)
Sweating increased	23 (10.5)	2 (2.2)
Cardiac murmur	22 (10.0)	8 (8.7)
Rhinorrhea	22 (10.0)	2 (2.2)
Gingival bleeding	21 (9.5)	4 (4.3)
Lymphadenopathy	21 (9.5)	3 (3.3)
Herpes simplex	20 (9.1)	5 (5.4)
Hematoma	19 (8.6)	0
Night sweats	19 (8.6)	3 (3.3)
Rales	19 (8.6)	8 (8.7)
Tachycardia	19 (8.6)	6 (6.5)
Wheezing	19 (8.6)	2 (2.2)
Cellulitis	18 (8.2)	4 (4.3)
Dysuria	18 (8.2)	2 (2.2)
Breath sounds decreased	17 (7.7)	1 (1.1)
Lethargy	17 (7.7)	2 (2.2)
Oral mucosal petechiae	17 (7.7)	3 (3.3)
Stomatitis	17 (7.7)	0

Preferred Term**	All Vidaza‡ (N=220)	Observation† (N=92)
At least 1 TEAE	219 (99.5)	89 (96.7)
Urinary tract infection	17 (7.7)	5 (5.4)
Peripheral swelling	16 (7.3)	5 (5.4)
Dyspepsia	15 (6.8)	4 (4.3)
Hemorrhoids	15 (6.8)	1 (1.1)
Hypotension	15 (6.8)	2 (2.2)
Injection site pruritus	15 (6.8)	0
Transfusion reaction	15 (6.8)	0
Pleural effusion	14 (6.4)	6 (6.5)
Abdominal distension	13 (5.9)	4 (4.3)
Muscle cramps	13 (5.9)	3 (3.3)
Post procedural hemorrhage	13 (5.9)	1 (1.1)
Postnasal drip	13 (5.9)	3 (3.3)
Rhonchi	13 (5.9)	2 (2.2)
Syncope	13 (5.9)	5 (5.4)
Urticaria	13 (5.9)	1 (1.1)
Anemia aggravated	12 (5.5)	5 (5.4)
Loose stools	12 (5.5)	0
Nasal congestion	12 (5.5)	1 (1.1)
Atelectasis	11 (5.0)	2 (2.2)
Chest wall pain	11 (5.0)	0
Dry skin	11 (5.0)	1 (1.1)
Dysphagia	11 (5.0)	2 (2.2)
Dyspnea exacerbated	11 (5.0)	3 (3.3)
Hypoesthesia	11 (5.0)	1 (1.1)
Injection site granuloma	11 (5.0)	0
Injection site pigmentation changes	11 (5.0)	0
Injection site swelling	11 (5.0)	0
Mouth hemorrhage	11 (5.0)	1 (1.1)
Post procedural pain	11 (5.0)	2 (2.2)
Sinusitis	11 (5.0)	3 (3.3)
Skin nodule	11 (5.0)	1 (1.1)
Tongue ulceration	11 (5.0)	2 (2.2)

** Mean Vidaza exposure = 11.4 months. Mean time in observation arm = 6.1 months.*

*** Multiple reports of the same preferred terms for a patient are only counted once within each treatment group.*

† Includes events from observation period only; excludes any events after crossover to Vidaza.

‡ Includes events from all patients exposed to Vidaza, including patients after crossing over from observation.

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