

## CLINICAL REVIEW

Application Type	sNDA [REDACTED] (b) (4)
Application Number(s)	21790 / S-014
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Division / Office	DHP / OHOP
Reviewer Name	Patricia Dinndorf, MD
Team Leader	Albert Deisseroth, MD PhD
Review Completion Date	6/22/12
Established Name	Decitabine
Trade Name	Dacogen
Therapeutic Class	Nucleoside analogue
Applicant	EISAI, Inc.
Formulation(s)	Lyophilized powder in a single-dose vial, 50 mg/vial
Dosing Regimen	Not applicable
Indication(s)	None
Intended Population(s)	None

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

(b) (4) The trial  
“A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects” accrued only 17 of the planned number of 40 patients. There was not enough data collected to assess activity or to inform a description of the pharmacokinetic parameters of decitabine in pediatric patients. There are no recommended changes to the pediatric use section of the label at this time.

### 1.2 Risk Benefit Assessment

There was not enough information collected in this trial to make a risk benefit assessment.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

### 1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Established Name:	Decitabine
Proprietary Name:	Dacogen
Applicant:	Eisai Inc.
Pharmacological Class:	Nucleoside analogue
Proposed Indication:	There is no proposed pediatric indication as a result of this trial.
Proposed Dosage and Administration:	There is no proposed dose or route of administration in pediatric patients as a result of this trial.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

There is no proposed indication in pediatric patients.

### 2.3 Availability of Proposed Active Ingredient in the United States

Decitabine is available as lyophilized powder in a single-dose vial, 50 mg/vial.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Decitabine is approved for the treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

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**Table 1: Regulatory History**

Regulatory History	
November 6, 1989	Original IND 33929 for treatment of leukemia submitted
November 1, 2004	Original NDA 21790 submitted
January 19, 2005	IND 71160 for patients with acute myeloid leukemia or myelodysplastic syndrome submitted
May 2, 2006	NDA 21790 Approved
July 9, 2008	Original Proposed Pediatric Study Request
August 19, 2008	FDA letter explaining deficiencies
October 20, 2008	Revised Proposed Pediatric Study Request
June 19, 2009	Original Written Request (Appendix 9.2)
January 26, 2010	Requests for Revisions <div style="background-color: black; width: 100%; height: 40px; margin-top: 5px;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>
April 22, 2010	Original protocol submitted to IND 71160 Revised 8/31/10 and 10/20/10
October 7, 2010	Revised Written Request (Appendix 9.3)
March 16, 2011	Final version of protocol submitted to IND 71160
October 5, 2011	Interim Report of Progress of study 12 Subjects
January 31, 2012	Study Report Written Request submitted n=17 Note. Written Request stipulated n=40

## 2.6 Other Relevant Background Information

The applicant is not seeking approval of decitabine for any pediatric indications.



### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

The submission contains the debarment certificate, sufficient datasets, and relevant CRFs. The overall quality and integrity of the submission is adequate to allow substantive review.

#### **3.2 Compliance with Good Clinical Practices**

The cover page of the Clinical Study Report has the following statement. "This study was performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation is archived as required by regulatory authorities."

#### **3.3 Financial Disclosures**

Form 3454 was submitted 3/13/12 and indicates that "No clinical investigators involved received compensation whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No clinical investigator involved disclosed a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b). No clinical investigator involved was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

Not applicable.

### **4.2 Clinical Microbiology**

Not applicable.

### **4.3 Preclinical Pharmacology/Toxicology**

Not applicable.

### **4.4 Clinical Pharmacology**

#### **4.4.1 Mechanism of Action (copied from label section 12.1 Mechanism of Action)**

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

#### **4.4.2 Pharmacodynamics**

See clinical pharmacology review.

#### **4.4.3 Pharmacokinetics**

See clinical pharmacology review.

## 5 Sources of Clinical Data

One trial was conducted in support of this application. This trial was conducted under IND 71160.

### 5.1 Tables of Studies/Clinical Trials

**Table 2: Synopsis of Trial Conducted to Support This Application**

Study Title	Endpoints	Study Population	Dose Regimen
A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects	Efficacy Analysis CR, time to CR, Leukemia free survival, OS	Primary AML in subjects 1 to 16 years of age.  Randomization 1:1 stratified by age: ~1 to < 2 yr ~2 to 11 yr ~12 to 16 yr  Minimum number of patients: ~1 to < 4 yr - 4 ~2 to 11 yr - 8 ~12 to 16 yr - 8	<u>Arm A</u> ~Decitabine 20 mg/m <sup>2</sup> IV infusion over 1 hour daily for 5 days (Days 1 to 5) ~Intrathecal Cytarabine (Day 1) ~Cytarabine 100 mg/m <sup>2</sup> /dose (3.3 mg/kg/dose if BSA < 0.6 m <sup>2</sup> ) IV push q 12 hrs x 10 days (Day 6 to Day 15) ~Daunorubicin 50 mg/m <sup>2</sup> /dose (1.67 mg/kg/dose if BSA < 0.6 m <sup>2</sup> ) IV infusion over 6 hrs x 3 days (Days 6, 8 and 10) ~Etoposide 100 mg/m <sup>2</sup> /dose (3.3 mg/kg/dose if BSA < 0.6 m <sup>2</sup> ) IV infusion over 4 hrs x 5 days (Days 6 to 10) <u>Arm B</u> ~Intrathecal Cytarabine (Day 1) ~Cytarabine (Day 1 to 10) ~Daunorubicin (Day 1, 3, 5) ~Etoposide (Day 1 to 5)

**Table 3: Participating Centers Enrolling Subjects**

Center ID	Investigator	Center
1002	Todd Cooper	Children's Healthcare of Atlanta/Emory University
1003	Lia Gore	The Children's Hospital, Denver CO
1006	Robert Arceci	Johns Hopkins Hospital, Baltimore MD
1010	Philip Barnette	Primary Children's Medical Center, Salt Lake City, UT
1015	Aru Narendran	Alberta Children's Hospital, Calgary, Alberta Canada
1016	Laura Martin	Nationwide Children's Hospital, Columbus, OH
1018	Carola Arndt	Mayo Clinic, Rochester, MN
1023	Wendy Tchong	Children's Hospital Central California, Madera CA
1101	Frank Alvaro	John Hunter Children's Hospital, New South Wales, Australia
1104	Francoise Mechinaud	The Royal Children's Hospital Melbourne, Melbourne, Australia

### 5.2 Review Strategy

The (b) (4) the study report submitted in this

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supplement was reviewed. The pediatric written request and an amended pediatric written requests are included in the appendix of this review See appendices 9.2 and 9.3.

### 5.3 Discussion of Individual Studies/Clinical Trials

#### 5.3.1 Study E7373-G2000-202 A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects

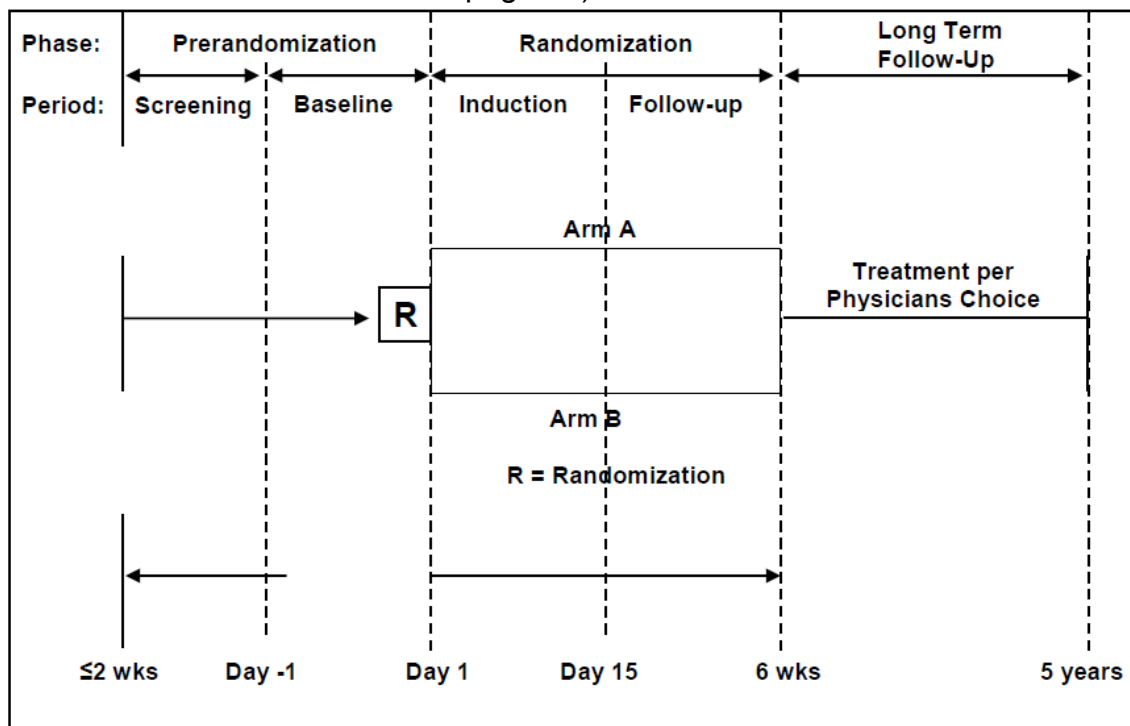
##### Schema

**Table 4: Study E7373-G2000-202**

Study Design	Multicenter, randomized, two-arm, open-label, parallel study with three phases: <ul style="list-style-type: none"><li>▪ Prerandomization</li><li>▪ Randomization</li><li>▪ Long-term Follow-up</li></ul>
Trial Opened to Subject Entry:	First subject entered March 2, 2011
Trial Closed to Entry:	Ongoing Last subject entered for this report October 27, 2011 Cut off date for data analysis November 29, 2011
Dose and Route:	Randomization to priming or no priming with decitabine Decitabine dose: 20 mg/m <sup>2</sup> IV infusion over 1 hour daily for 5 days (Days 1 to 5)
Indication:	Newly diagnosed AML
Planned enrollment:	40 total; 20 decitabine priming; 20 no priming There were to be 3 subsets of age groups: <ul style="list-style-type: none"><li>▪ 1 to &lt; 2 years (minimum 4)</li><li>▪ 2 to 11 years (minimum 8)</li><li>▪ 12 to 16 years (minimum 8)</li></ul>
Actual enrollment:	17 total; 8 decitabine priming; 9 no priming
Terminated early (YES/NO):	Study ongoing but study report submitted prior to complete accrual to meet the Written Request deadline

**Figure 1: Study Schema**

(copied from submission eCTD (b) (4) Section 5.3.5.2.4 Protocol E7373-G000-202 page 20)



**Study Objectives:**

**Primary objective**

To evaluate the short term efficacy of decitabine when used as priming before induction chemotherapy in pediatric AML subjects.

**Secondary objectives**

- To evaluate the safety of decitabine when used as priming before induction chemotherapy in pediatric AML subjects
- To evaluate the pharmacokinetics of decitabine in pediatric AML subjects receiving decitabine as priming before induction chemotherapy
- To evaluate DNA methylation and exploratory biomarkers in pediatric AML subjects receiving decitabine priming before induction chemotherapy
- To evaluate time to platelet recovery ( $\geq 100,000/\text{mm}^3$ ) and time to neutrophil recovery (absolute neutrophil count [ANC]  $\geq 1000/\text{mm}^3$ ) following induction chemotherapy
- To evaluate minimal residual disease in pediatric AML subjects receiving decitabine priming before induction chemotherapy.
- To evaluate the long term efficacy of decitabine when used as priming before induction chemotherapy in pediatric AML subjects during long term follow-up.

## **Eligibility Criteria:**

### **Inclusion Criteria**

- Males and females, age 1 to 16 years, inclusive
- Females of childbearing potential must have a negative serum  $\beta$ -hCG at Visit 1 (Screening) and a negative urine pregnancy test prior to starting study drugs (Visit 2). Female subjects of childbearing potential must agree to be abstinent or to use a highly effective method of contraception (e.g., condom + spermicide, condom + diaphragm with spermicide, intrauterine device (IUD), or have a vasectomised partner) for at least one menstrual cycle prior to starting study drug(s) and throughout the Randomization Phase or 30 days after the last dose of study drug. Those females using hormonal contraceptives must also be using an additional approved method of contraception (as described previously)
- Sexually mature male patients who are not abstinent or have not undergone a successful vasectomy, who are partners of women of childbearing potential must use, or their partners must use a highly effective method of contraception (e.g., condom + spermicide, condom + diaphragm with spermicide, IUD) starting for at least one menstrual cycle prior to starting study drug(s) and throughout the Randomization Phase and for 30 days (longer if appropriate) after the last dose of study drug. Those with partners using hormonal contraceptives must also be using an additional approved method of contraception (as described previously)
- Diagnosis of primary AML (bone marrow or peripheral blood blasts  $\geq 20\%$ )
- Adequate cardiac function as defined by an echocardiogram or multiple gated acquisition (MUGA) scan demonstrating an ejection fraction  $> 50\%$  or a shortening fraction of  $> 26\%$
- Are willing and able to comply with all aspects of the protocol
- Provide written informed consent from subject's guardian or legally authorized representative and child assent (if applicable).

### **Exclusion Criteria:**

- Females who are pregnant (positive  $\beta$ -hCG test) or lactating
- History of chronic myelogenous leukemia (CML) [t(9;22)]
- Acute promyelocytic leukemia (M3 subtype in French-American-British [FAB] classification)
- Clinically symptomatic CNS disease
- AML associated with congenital syndromes such as Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, or Diamond-Blackfan anemia
- White blood cell (WBC) count  $> 100,000/\text{mm}^3$
- Serum creatinine  $> 2.5 \text{ mg/dL}$
- Alanine aminotransferase (ALT)  $> 5 \times$  upper limit of normal (ULN), aspartate aminotransferase (AST)  $> 5 \times$  ULN, and/or total bilirubin  $> 3 \times$  ULN
- Prior chemotherapy (other than hydroxyurea) or radiation therapy for AML
- Known to be human immunodeficiency virus (HIV) positive

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- Any history of or concomitant medical condition that, in the opinion of the Investigator, would compromise the subject's ability to safely complete the study
- The Investigator believes the subject to be medically unfit to receive the study drug or unsuitable for any other reason
- Subject with hypersensitivity to decitabine, daunorubicin, cytarabine, or etoposide
- Has participated in a drug trial in the last 4 weeks.

REVIEWER COMMENT

Review of the documentation of initial bone marrow results identifies 3 subjects without documentation of bone marrow or peripheral blood blasts  $\geq 20\%$ . (1003-1003 Arm A, 1104-1001 Arm A, 1104-1002 Arm B)

**Demographics and Baseline Characteristics**

Table 5: Demographics and Baseline Characteristics

<b>Demographics and Baseline Characteristics</b>			
	Arm A (n= 8)	Arm B (n=9)	Total (n=17)
<b>Gender</b>			
Male	3	5	8
Female	5	4	9
<b>Age in Years</b>			
1 - < 2		1	1
2 - 11	4	3	7
12 - 16	4	5	9
Mean	10.4	10.0	10.2
Median	12	12	12
Range	2 - 16	1 -16	1 - 16
<b>Race Ethnicity</b>			
White Non-Hispanic	6	7	13
White Hispanic		2	2
Black or African American	1		1
American Indian or Alaskan Native	1		1
<b>AML FAB Classification</b>			
M0	1	1	2
M1	1		1
M2	2	5	7
M4	2	1	3
M5	1	1	2
M7		1	1
unclassified	1		1

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## Disposition

**Table 6: Patient Disposition**

(copied from submission eCTD (b) (4) Section  
5.3.5.1.3 Study Report Body page 48)

Parameter Statistic	Arm A  (Decitabine + Induction Chemotherapy)	Arm B  (Induction Chemotherapy Alone)
Randomized, n (%)	8 (100)	9 (100)
Treated, n (%)	8 (100)	9 (100)
Completed Day 35 posttreatment visit, n (%)	7 (87.5)	9 (100)
Treatment ongoing, n (%)	0	0
Treatment discontinued, n (%)	1 (12.5)	0
Primary reason for discontinuation, <sup>a</sup> n (%)		
Adverse event <sup>b</sup>	1 (12.5)	0

<sup>b</sup>One subject 1018-1001, who was assigned to Arm A, had two SAEs; namely, appendicitis and large intestine perforation. The subject received 5 days' treatment with decitabine and one infusion of cytarabine 140 mg before study treatment was permanently discontinued on Study Day 6. The subject was taken to surgery for an appendectomy and ileostomy placement. The final pathology report indicated acute appendicitis and serositis, with AML involvement in the appendix and regional lymph nodes of the colon. Morphologically, the lymphoid tissue of the appendix and the lymph node showed focal infiltrate of immature myeloid cells.

## Exposure

### Decitabine

All subjects randomized to Arm A received 100%  $\pm$  2 of the protocol directed dose of decitabine.

### Intrathecal Cytosine Arabinoside.

All 17 subjects received the age appropriate dose of intrathecal cytosine arabinoside.

### Systemic Induction Chemotherapy

All subjects received 100%  $\pm$  3 of the protocol directed chemotherapy with the exception of 1018-1001 described in the note under Table 6: Patient Disposition.



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## Results

### Efficacy Evaluation

#### Induction Remission Rate

Induction Remission Rate was the primary efficacy analysis of this study. These results are summarized in Table xx below.

**Table 7: Induction Remission Rate**

n (%)	Arm A n=8	Arm B n=9
Complete remission (CR)	2 (25)	6 (67)
Complete remission incomplete count recover (CRi)	4 (50)	1 (11)
Combined CR and CRi	6 (76)	7 (79)
Did not receive induction therapy due to AE	1 (13)	
Bone marrow evaluation not performed		1 (11)

Additional follow up regarding the induction remission rate was included in the study report. [derived from submission eCTD (b) (4) Section 5.3.5.1.3 Study Report Body page 55]

- Subject 1003-1004 who did not have a bone marrow evaluation at the designated time point subsequently had a documented bone marrow in remission.
- Four (3 in Arm A and 1 in Arm B) of the five subjects with CRi at the Visit 6 time point subsequently had recovery of their peripheral counts, consistent with a classification of CR

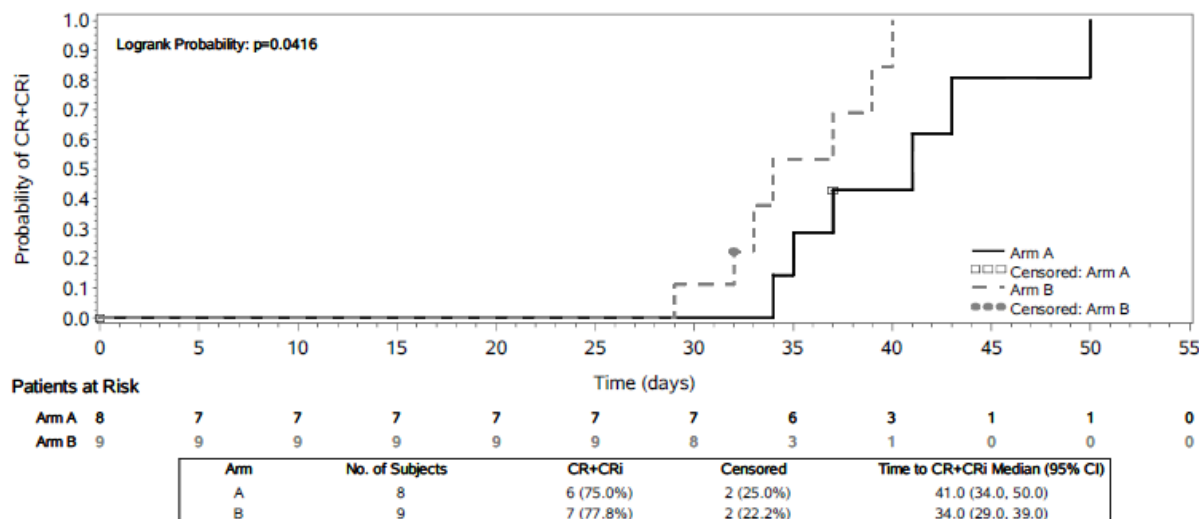
The updated remission rates were Arm A 75% (n=6/8) and Arm B 88.9% (n=8/9). When the results from the subject whose bone marrow sample was obtained after the data cutoff date were included with those subjects who achieved a CR or CRi by Visit 6, the data suggest that there is an 81% likelihood of not observing a difference in CR rates between the two arms after all 40 subjects are enrolled.

#### Secondary Clinical Analysis

Time to CR (copied from submission eCTD (b) (4) Section 5.3.5.1.3 Study Report Body page 177)

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Figure 2: Kaplan-Meier Plot of Time to CR + CRi



DNA Methylation (copied from submission eCTD (b) (4))

Section 5.3.5.1.3 Study Report Body page 58)

DNA methylation was evaluated in Arm A at various time points during the study. A total of 85 samples have been received and the DNA isolated. Results will be provided in a separate bioanalytical report at the completion of the study.

Time to Neutrophil/Platelet Recovery (copied from submission eCTD (b) (4))

Section 5.3.5.1.3 Study Report Body page 59)

Table 8: Kaplan-Meier Analysis of Times to Platelet and Neutrophil Recovery

	Arm A	Arm B
	Decitabine + Induction Chemotherapy (N=8)	Induction Chemotherapy Alone (N=9)
<b>Time to Platelet Recovery (to <math>\geq 100,000/\text{mm}^3</math>), days</b>		
Number of subjects with recovery	8	9
Number of subjects not recovered	0	0
Median (95% CI)	21.0 (2, 23)	9.0 (2, 23)
1st quartile (95% CI)	13.5 (2, 21)	8.0 (2, 9)
3rd quartile (95% CI)	22.5 (21, 31)	22.0 (8, 24)
Min, Max	2.0, 31.0	2.0, 24.0
<b>Time to Neutrophil Recovery (to ANC <math>\geq 1000/\text{mm}^3</math>), days</b>		
Number of subjects with recovery	7	8
Number of subjects not recovered	1	1
Median (95% CI)	21.0 (2, 43)	17.5 (15, 25)
1st quartile (95% CI)	16.5 (2, 21)	15.5 (15, 18)
3rd quartile (95% CI)	35.5 (20, 43)	22.5 (16, 39)
Min, Max	2, 43	9+, 39

Minimal residual disease was assessed at (b) (4). Viable samples were obtained at both baseline and end of treatment for 6 (35.3%) of the 17 subjects as shown in Table 9. All of these subjects were in the decitabine (Arm A) group. However, five additional subjects had an evaluable bone marrow sampling at end of treatment.

**Table 9: Minimal Residual Disease Evaluation**

Subject ID	Baseline	End of Treatment
<b>Treatment Arm A</b>		
1003-1003	10%	0%
1006-1001	8%	0%
1006-1002	1%	0%
1006-1003	76%	0%
1006-1004 <sup>a</sup>	20%	15%
1015-1001	32%	0.1%
1018-1001 <sup>b</sup>	NA	NA
1104-1001	NA	0%
<b>Treatment Arm B</b>		
1002-1001	NA	0%
1003-1001	NA	NA
1003-1002	NA	NA
1003-1004	NA	0%
1010-1001	NA	0%
1016-1001	NA	NA
1023-1001	NA	0.4%
1101-1001	NA	0%
1104-1002	NA	NA

Survival (copied from submission eCTD (b) (4) Section 5.3.5.1.3 Study Report Body page 60)

Following completion or discontinuation of study treatment, all subjects are being followed for survival. As of the clinical cutoff date, no subject had died and no subject who achieved a CR had relapse of leukemia. Therefore, as of the cutoff date, overall survival was 100%.

Three subjects (Arm A: n=2; Arm B, n=1) did not achieve a CR or CRi as of the clinical cutoff date and were considered to be treatment failures for the leukemia free survival analysis.

For completeness of review, one subject (1006-1001) in Arm B died after the clinical cutoff date. This subject died of a cerebral hemorrhage 5 months after end of treatment (data on file). This subject had achieved a CRi.

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Pharmacokinetic Evaluation (copied from submission eCTD (b) (4)

Section 5.3.5.1.3 Study Report Body page 62)

All samples received as of 18 Nov 2011 have been included in the PK analyses. At that time point, the sponsor had obtained samples from all eight decitabine-treated subjects.

**Table 10: Pharmacokinetic Parameters of Decitabine on Day 5 of Treatment**

Pharmacokinetic Parameter	Age Group (y)		Arm A Total (N=8)	Comparator 70-kg Adult Male
	2 - 11 (N=4)	12 - 16 (N=4)		
$C_{max}$ (ng/mL)	255 (164)	307 (36.9)	281 (113)	107
$t_{max}$ (h)	0.760 <sup>a</sup>	0.925 <sup>a</sup>	0.925 <sup>a</sup>	NR
$t_{1/2}$ (h)	0.49 (0.061)	0.46 (0.064)	0.48 (0.060)	1.14
$AUC_{0-t}$ (ng•h/mL)	179 (89.2)	216 (33.5)	197 (65.4)	NR
$AUC_{0-\infty}$ (ng•h/mL)	180 (88.7)	217 (33.9)	198 (65.3)	580 <sup>b</sup>
CL (L/h)	150 (142)	162 (22.8)	156 (94.6)	298
$Vd_{ss}$ (L)	109 (104)	108 (23.7)	109 (70.0)	116

Estimated PK values for a typical 70-kg adult male receiving decitabine 20 mg/m<sup>2</sup> as a 1-hour infusion are included as a reference. The mean exposure to decitabine, as measured by  $C_{max}$  and AUC, was marginally higher in the 12- to 16-year age category compared with the 2- to 11-year age category. However, intersubject variability was high, and the higher values in the 12- to 16-year age category were due to only one outlying subject.

See clinical pharmacology reviewer for FDA evaluation of this data.

#### Safety Evaluation

See Section 7.

#### **Conclusions**

There is no indication from this small experience that priming with decitabine prior to AML induction therapy improves the remission induction rate of pediatric AML patients.

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## 6 Review of Efficacy

### **Efficacy Summary**

The applicant is not submitting any data that supports efficacy. A review of Study E7373-G2000-202 “A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects” is presented in section 5.3. This study had not reached full accrual at the time of submission. However, analysis of the data available to date suggests it is unlikely that priming with decitabine prior to AML induction therapy will improve the remission induction rate of pediatric patients with AML.

## 7 Review of Safety

### **Safety Summary**

The adverse events reported in this study were adverse events expected in the study population, that is patients with newly diagnosed leukemia undergoing induction chemotherapy. There were no significant safety signals identified in the decitabine treated patients.

### 7.1 Methods

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

**Table 11: Trial Conducted to Support This Application**

Study Title	Endpoints	Study Population	Dose Regimen
A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Decitabine as Epigenetic Priming With Induction Chemotherapy in Pediatric Acute Myelogenous Leukemia (AML) Subjects	Efficacy Analysis CR, time to CR, Leukemia free survival, OS	Primary AML in subjects 1 to 16 years of age.  Randomization 1:1 stratified by age: ~1 to < 2 yr ~2 to 11 yr ~12 to 16 yr  Minimum number of patients: ~1 to < 4 yr – 4 ~2 to 11 yr - 8 ~12 to 16 yr - 8	<u>Arm A</u> ~Decitabine 20 mg/m <sup>2</sup> IV infusion over 1 hour daily for 5 days (Days 1 to 5) ~Intrathecal Cytarabine (Day 1) ~Cytarabine 100 mg/m <sup>2</sup> /dose (3.3 mg/kg/dose if BSA < 0.6 m <sup>2</sup> ) IV push q 12 hrs x 10 days (Day 6 to Day 15) ~Daunorubicin 50 mg/m <sup>2</sup> /dose (1.67 mg/kg/dose if BSA < 0.6 m <sup>2</sup> ) IV infusion over 6 hrs x 3 days (Days 6, 8 and 10) ~Etoposide 100 mg/m <sup>2</sup> /dose (3.3 mg/kg/dose if BSA < 0.6 m <sup>2</sup> ) IV infusion over 4 hrs x 5 days (Days 6 to 10) <u>Arm B</u> ~Intrathecal Cytarabine (Day 1) ~Cytarabine (Day 1 to 10) ~Daunorubicin (Day 1, 3, 5) ~Etoposide (Day 1 to 5)

#### 7.1.2 Categorization of Adverse Events

Adverse Events were recorded in the CRF and graded according to CTCAE v4. All Adverse Events terms in CTCAE version 4.0 were correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA), version 14.0.

#### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The data from CI18083/2046 was the only data derived from a clinical trial included. The submission does not include an integrated safety summary. The Periodic Safety Update

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Report covering May 2, 2001 to November 1, 2011 was included to satisfy the requirement that the submission include postmarketing adverse event reports.

## 7.2 Adequacy of Safety Assessments

The safety assessments appear to have been collected and categorized adequately. A comparison was done of the verbatim term (AETERM) and the preferred term (AEDECOD) and the categorization of the verbatim term was appropriate.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

See Section 5.3.1.

### 7.2.2 Explorations for Dose Response

Not done.

### 7.2.3 Special Animal and/or In Vitro Testing

Not done.

### 7.2.4 Routine Clinical Testing

CBCs, Chemistries including bilirubin, transaminases, alk phos, electrolytes, creatinine, glucose, were collected.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not done.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No analysis done.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths.

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### 7.3.2 Nonfatal Serious Adverse Events

There was 1 subject 1018-1001, who was assigned to Arm A, had two serious adverse events; namely, appendicitis and large intestine perforation. The subject received 5 days' treatment with decitabine and one infusion of cytarabine 140 mg before study treatment was permanently discontinued on Study Day 6. The subject was taken to surgery for an appendectomy and ileostomy placement. The final pathology report indicated acute appendicitis and serositis, with AML involvement in the appendix and regional lymph nodes of the colon. Morphologically, the lymphoid tissue of the appendix and the lymph node showed focal infiltrate of immature myeloid cells.

### 7.3.3 Dropouts and/or Discontinuations

The only subject who discontinued the study early was 1018-1001 discussed in 7.3.2.

### 7.3.4 Significant Adverse Events

A summary of Grade 3 and 4 adverse events that occurred in two or more subject are presented in the following table. (copied from submission eCTD (b) (4)

Section 5.3.5.1.3 Study Report Body page 71)



**Table 12: Grade 3 and 4 Adverse Events**

MedDRA SOC Preferred Term	Arm A			Arm B		
	Decitabine + Induction Chemotherapy (N=8)			Induction Chemotherapy Alone (N=9)		
	Grade 3	Grade 4	Grade 3+4	Grade 3	Grade 4	Grade 3+4
Total n (%) of subjects with Grade 3-4 TEAE	7 (87.5)	7 (87.5)	8 (100)	7 (77.8)	7 (77.8)	8 (88.9)
<b>Blood and Lymphatic System Disorders</b>	<b>7 (87.5)</b>	<b>5 (62.5)</b>	<b>7 (87.5)</b>	<b>5 (55.6)</b>	<b>3 (33.3)</b>	<b>6 (66.7)</b>
Anemia	6 (75.0)	2 (25.0)	6 (75.0)	4 (44.4)	1 (11.1)	4 (44.4)
Febrile neutropenia	1 (12.5)	0	1 (12.5)	4 (44.4)	0	4 (44.4)
Neutropenia	1 (12.5)	3 (37.5)	3 (37.5)	1 (11.1)	1 (11.1)	1 (11.1)
Thrombocytopenia	4 (50.0)	4 (50.0)	4 (50.0)	0	2 (22.2)	2 (22.2)
<b>Gastrointestinal Disorders</b>	<b>4 (50.0)</b>	<b>1 (12.5)</b>	<b>5 (62.5)</b>	<b>1 (11.1)</b>	<b>1 (11.1)</b>	<b>2 (22.2)</b>
Caecitis	2 (25.0)	0	2 (25.0)	0	0	0
Stomatitis	0	0	0	1 (11.1)	1 (11.1)	2 (22.2)
<b>Investigations</b>	<b>6 (75.0)</b>	<b>6 (75.0)</b>	<b>6 (75.0)</b>	<b>4 (44.4)</b>	<b>6 (66.7)</b>	<b>6 (66.7)</b>
Lymphocyte count decreased	1 (12.5)	1 (12.5)	1 (12.5)	1 (11.1)	0	1 (11.1)
Neutrophil count decreased	0	0	0	1 (11.1)	3 (33.3)	3 (33.3)
Platelet count decreased	0	1 (12.5)	1 (12.5)	2 (22.2)	3 (33.3)	3 (33.3)
White blood cell count decreased	6 (75.0)	6 (75.0)	6 (75.0)	3 (33.3)	5 (55.6)	5 (55.6)
<b>Metabolism and Nutrition Disorders</b>	<b>4 (50.0)</b>	<b>1 (12.5)</b>	<b>4 (50.0)</b>	<b>1 (11.1)</b>	<b>0</b>	<b>1 (11.1)</b>
Decreased appetite	3 (37.5)	0	3 (37.5)	0	0	0
Hypokalaemia	3 (37.5)	0	3 (37.5)	1 (11.1)	0	1 (11.1)
Hypophosphataemia	2 (25.0)	0	2 (25.0)	0	0	0
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>3 (37.5)</b>	<b>0</b>	<b>3 (37.5)</b>	<b>1 (11.1)</b>	<b>0</b>	<b>1 (11.1)</b>
Alopecia	2 (25.0) <sup>a</sup>	0	2 (25.0)	0	0	0

The most common grade 3 and 4 adverse events reported were cytopenias. Sixteen subjects (Arm A - n=7, Arm B - n=9) were reported to have grade 3 or 4 either as an adverse event or as part of the routine laboratory evaluation.

### 7.3.5 Submission Specific Primary Safety Concerns

No specific safety concerns were identified.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

As labeled, the most common adverse reactions (> 50%) associated with decitabine are neutropenia, thrombocytopenia, anemia, and pyrexia.

The adverse events that were reported as treatment related are presented in the following table. (copied from submission eCTD (b) (4) Section 5.3.5.1.3 Study Report Body page 74).

**Table 13: Treatment Related Adverse Events (in more than 1 subject)**

MedDRA SOC Preferred Term	Arm A
	Decitabine + Induction Chemotherapy (N=8)
Total n (%) of subjects with related TEAE	6 (75.0)
<b>Blood and Lymphatic System Disorders</b>	<b>6 (75.0)</b>
Anemia	5 (62.5)
Neutropenia	2 (25.0)
Thrombocytopenia	3 (37.5)
<b>Gastrointestinal Disorders</b>	<b>5 (62.5)</b>
Nausea	2 (25.0)
<b>General Disorders and Administration Site Conditions</b>	<b>2 (25.0)</b>
Pyrexia	2 (25.0)
<b>Investigations</b>	<b>5 (62.5)</b>
White blood cell count decreased	5 (62.5)
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>4 (50.0)</b>
Alopecia	2 (25.0)
Petechiae	2 (25.0)
Rash	2 (25.0)

#### 7.4.2 Laboratory Findings

##### Hematology

Sixteen subjects (Arm A - n=7, Arm B - n=9) were reported to have grade 3 or 4 cytopenias as part of the routine laboratory evaluation of CBCs.

##### Chemistry

**Table 14: Per Patient Abnormalities in Liver and Renal Laboratory Parameters**

	Arm A n=8	Arm B n=9
Liver Abnormalities ≥ Grade 2 AST, ALT, Bilirubin	1	3
Grade 2 Creatinine	1	0

#### 7.4.3 Vital Signs

No analysis done.

#### 7.4.4 Electrocardiograms (ECGs)

ECGs were not performed as a component of this study.

#### 7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

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7.4.6 Immunogenicity

No allergic reactions related to decitabine were reported.

## 7.5 Other Safety Explorations

These were not analyzed.

## 7.6 Additional Safety Evaluations

These were not analyzed.

## **8 Postmarket Experience**

The applicant submitted a Periodic Safety Update Report (PSUR) covering 5/2/11 through November 2011 to address the postmarketing experience. No adverse events were identified in the PSUR submission that would change the risk-benefit assessment of decitabine (Dacogen). Review of the PSUR was entered into DARRTS as a separate report.

## 9 Appendices

### 9.1 Labeling Recommendations

No changes to the label are indicated based on this submission.

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This application was discussed

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/s/  
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