Clinical Pharmacology Review

NDA	21-790/SDN294; SDN305
Submission Date:	1/31/12; 3/26/12
Brand Name:	Dacogen®
Generic Name:	Decitabine
Formulation:	Injection
OCP Reviewer:	Young Jin Moon, Ph.D.
OCP Acting Team Leader:	Bahru Habtemariam, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Hematology Products
Sponsor:	Eisai Inc.
Submission Type; Code:	Supplemen (b) (4)
Dosing regimen:	Option 1: 15 mg/m by 3 hrs infusion repeated every 8 hrs for 3 days. Repeat cycle every 6 weeks Option 2: 20 mg/m^2 by 1 hr infusion repeated daily for 5 days. Repeat cycle every 4 weeks
Indication:	Myelodysplastic syndromes (MDS)

1 EXECUTIVE SUMMARY

Decitabine is currently approved for the treatment of patients with myelodysplastic syndromes (MDS). This submission includes a study report for protocol E7373-G000-202 entitled, "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". (b) (4) Out of 59 patients screened, 17 were enrolled and treated, and the current report summarizes interim study data for the 17 patients. (b) (4) No labeling changes were proposed.

Study E7373-G000-202 (DACO-202) was a randomized, two-arm, parallel design, phase 2 trial to compare remission rate when induction chemotherapy was given with decitabine priming (Arm A) and without decitabine priming (Arm B). The primary endpoint was morphologic complete remission (CR) rate. Two subjects (25%) in Arm A and 6 subjects (66.7%) in Arm B achieved a CR as of the clinical cutoff date. The total remission rate (CR+CRi) was 75% (n=6/8) for Arm A and 77.8% (n=7/9) for Arm B. As of the clinical cutoff date, there was no conclusive difference in efficacy between the treatment arms based on remission rates and no deaths had occurred. The safety profile of Arm A appeared similar to Arm B and the expected safety profile of induction chemotherapy in children. No new safety signals for decitabine were observed.

Decitabine pharmacokinetic (PK) data were obtained from 8 children ages 2-16; 2-11 years (N=4) and 12-16 years (N=4) age. The PK parameters of decitabine were highly variable in children ages 2-11 years old. There were no PK data in children ages 1-2. Therefore, due to the limited number of subjects and absence of PK data in children ages 1-2, no conclusions can be made regarding the influence of age on the PK of decitabine.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information submitted in sNDA 21-790 (SDN294) (b) (4) . The submitted pediatric clinical study, which was conducted under a written request agreement, did not adhere to the written request agreement. The submitted study enrolled fewer patients (n=17) than what was agreed in the written request (n=40). In addition, the pharmacokinetics of decitabine was not adequately characterized in children ages 1-16 due to very small sample size (n=8).

(b) (4)

(b) (4)

Signatures:

Reviewer: Young Jin Moon, Ph.D. Division of Clinical Pharmacology 5	Acting Team Leader: Bahru Habtemariam, Pharm.D. Division of Clinical Pharmacology 5

Cc: DHP: CSO - M Cato; MTL - A Deisseroth; MO - P Dinndorf
DCP-5: Reviewer - Y Moon; ATL – B Habtemariam
DDD - B Booth ; DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

Decitabine (MW=228) is a cytotoxic, DNA methylation inhibitor. Approved dosing regimens are Option 1: 15 mg/m^2 administered by continuous intravenous (IV) infusion over 3 hours, repeated every 8 hours for 3 days, cycle repeated every 6 weeks; and Option 2: 20 mg/m^2 administered as a 1-hour IV infusion once daily, on 5 consecutive days, cycle repeated every 4 weeks. For the present submission the option two dosing regimen was used where 20 mg/m^2 of decitabine was administered as a 1-hour IV infusion once daily for 5 days. The PK parameters of decitabine were calculated and categorized into two age groups: 2-11 years old (N=4) and 12-16 years old (N=4). High variability in decitabine PK parameters was observed among subjects with 2-11 years old (see **Table 2**), whereas variability was relatively low in 12-16 years of age group (see **Table 2**). There did not appear to be an age-related trend and decitabine PK appeared to be similar between pediatric and adult patients. However, due small sample size, no conclusion can be made regarding the effect of age on the PK of decitabine.

2 QUESTION BASED REVIEW

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of clinical studies used to support dosing or claims?

Study E7373-G000-202 (DACO-202) was a multicenter, randomized, two-arm, open-label, parallel design, phase 2 study. In this study decitabine was studied as an epigenetic priming agent following decitabine doses of 20 mg/m^2 once daily for 5 days administered as intravenous infusion immediately before induction chemotherapy. Patients in Arm A received all four study treatments (decitabine priming for 5 days followed by daunorubicin, cytarabine, and etoposide induction chemotherapy over 10 days) and subjects in Arm B received induction chemotherapy with daunorubicin (Days 1, 3, and 5), cytarabine (Days 1-10), and etoposide (Days 1-5) over 10 days without decitabine priming. The dosage of decitabine used as priming in this study, 20 mg/m^2/day for 5 days, is widely used in adult patients with AML and has demonstrated sufficient DNA hypomethylation.

(b) (4)

(b) (4)

2.2.7 What are the single dose and multiple dose PK parameters?

Blood samples for the PK analysis were drawn in all eight subjects in Arm A on Day 5 immediately before the start of the decitabine infusion (pre-dose) and at 30 minutes, 60 minutes (immediately before the end of infusion), 65 minutes, 90 minutes, 2 hours, and 3 hours after the start of the infusion. PK parameters of decitabine in pediatric patients by age group and those obtained in adult study (DACO-020) are shown in **Table 2**. Individual values of total exposure (AUC_{inf}) in pediatric and adult patients are presented in **Figure 1**.

Table 2. Mean Pharmacokinetic Parameters of Decitabine on Day 5 of Treatment—Overall and by Age Group, Pharmacokinetic Analysis Population

PK parameter	Age group (y) (CV%)		Adult data from label (N=11; DACO-020)
	2-11 (N=4)	12-16 (N=4)	
C_{max} (ng/mL)	255 (64)	307 (12)	147 (49)
T_{max} (h)	0.76	0.925	NP
$T_{1/2}$ (h)	0.49 (12)	0.46 (14)	0.54 (43)
AUC_{0-t} (ng·h/mL)	179 (50)	216 (16)	NP
$AUC_{0-\infty}$ (ng·h/mL)	180 (50)	217 (16)	115 (43)
CL (L/h)	150 (95)	162 (14)	210 (47)
Vd_{ss} (L)	109 (95)	108 (22)	NP

NP: not reported

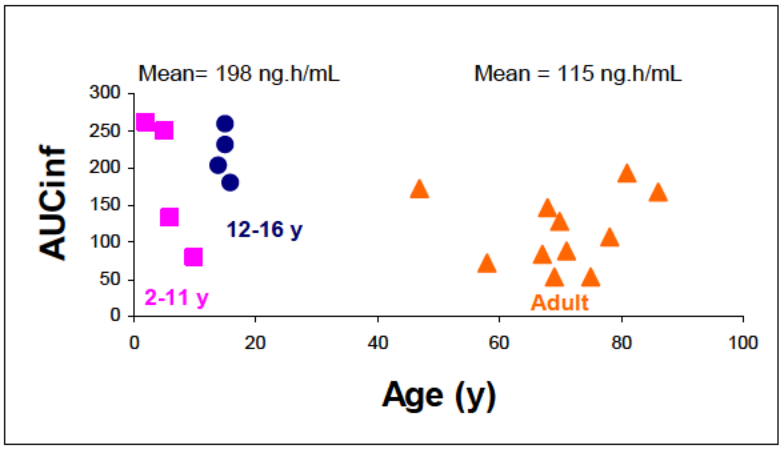

Figure 1. Individual values of total exposure (AUC_{inf}) by age

High variability in decitabine PK parameters was observed among subjects with 2-11 years old, whereas variability was relatively low in 12-16 years of age group (**Table 2**). There did not appear to be an age-related trend and decitabine PK appeared to be similar between pediatric and adult patients. However, due to the limited number of subjects, no conclusion can be made regarding the effect of age on the PK of decitabine.

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess concentrations?

Concentrations of decitabine in human plasma samples were simultaneously determined by (b) (4) during 17-Oct-2011 through 29-Nov-2011 using a validated high-performance liquid chromatography method with tandem mass spectrometric detection. All samples were analyzed within the sample storage stability. The methods appear generally acceptable.

Table 3. LC-MS/MS bioassay for Decitabine (Report 02815)

Information Requested	**Data**
Bioanalytical method validation report location	Report 00750
Analytes	Decitabine
Internal standard	(b) (4)
Standard curve concentrations (ng/mL)	1.00 to 100.00 ng/mL
QC concentrations (ng/mL)	3.00, 40.0, 90.0 ng/mL
QC intra- and inter-assay accuracy (%)	94.1-98.0%
QC intra- and inter-assay precision (%)	4.91-8.43%
Shipment condition	Frozen on dry ice
Storage temperature	-70°C
Number of samples	104 (56 primary and 48 backup samples)
Long-term storage stability	At least 370 days at -70°C

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/s/

YOUNG J MOON
06/20/2012

BAHRU A HABTEMARIAM
06/20/2012