European Medicines Agency
SCIENCE MEDICINES HEALTH

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Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Dacogen

decitabine

Procedure no: EMEA/H/C/002221/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

1. Introduction

On 16 February 2016, the MAH submitted the final study report of a completed paediatric study E773-G000-202 for decitabine, in context of Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH acknowledges that this Article 46 submission is outside of the usual six months period after completion of a pediatric study. Indeed, the end of trial date for this study was 19th July 2013 (final clinical cut-off date).

The MAH submitted two separate CSR:

- an interim CSR dated on 19th January 2012

- an CSR Addendum dated on 23rd September 2015.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study E7373-G000-202 "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" was conducted exclusively by its business partner, Eisai Inc and is not part of the MAH development programme.

As such this study is considered a stand-alone study and is not listed as a clinical measure in the MAH PIP for Dacogen.

2.2. Information on the pharmaceutical formulation used in the study

NA

2.3. Clinical aspects

2.3.1. Introduction

The assessment is essentially based on the resulted in the CSR Addendum dated on 23rd September 2015 for Study E7373-G000-202 "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." (named Daco-202 in this report).

2.3.2. Clinical study

Description

It is hypothesized that pretreatment (i.e., priming) with a hypomethylating agent will increase the efficacy of induction chemotherapy for AML. In this study DACO-202, decitabine was studied as an epigenetic priming agent using the regimen of a 1-hour intravenous (IV) infusion of 20 mg/m2 once daily for 5 days, immediately before induction chemotherapy. This dosage was chosen based on (1)

the large amount of safety data collected on the regimen in clinical trials in adults, and (2) data that show a 1-hour infusion of decitabine 20 mg/m2 is sufficient to inhibit DNA methyltransferase and induce tumor suppressor gene activation as early as 3 to 5 days after treatment initiation. This study aimed to provide data on the activity of a standard induction regimen (cytarabine, daunorubicin, and etoposide) plus epigenetic priming with decitabine as assessed by standard measures of morphologic CR, leukemia-free survival (LFS), overall survival (OS), and incidence of minimal residual disease (MRD).

Methods

Objectives

Primary objective:

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

Secondary objectives:

- To evaluate the safety of decitabine

- To evaluate the pharmacokinetics (PK) of decitabine

- To evaluate DNA methylation and exploratory biomarkers in pediatric subjects with AML receiving decitabine priming before induction chemotherapy

- To evaluate time to platelet recovery (≥ 100,000/mm3) and neutrophil recovery (absolute neutrophil count [ANC] ≥ 1000/mm3) after induction chemotherapy

- To evaluate minimal residual disease (MRD) in pediatric subjects with AML receiving decitabine priming

- before induction chemotherapy

- To evaluate the long-term efficacy of decitabine

Exploratory objective:

- To to evaluate potential biomarkers predictive of a positive therapeutic response in pediatric subjects with AML receiving decitabine priming before induction chemotherapy

Study design

This is a multicenter, randomized, two-arm, open-label, parallel design study.
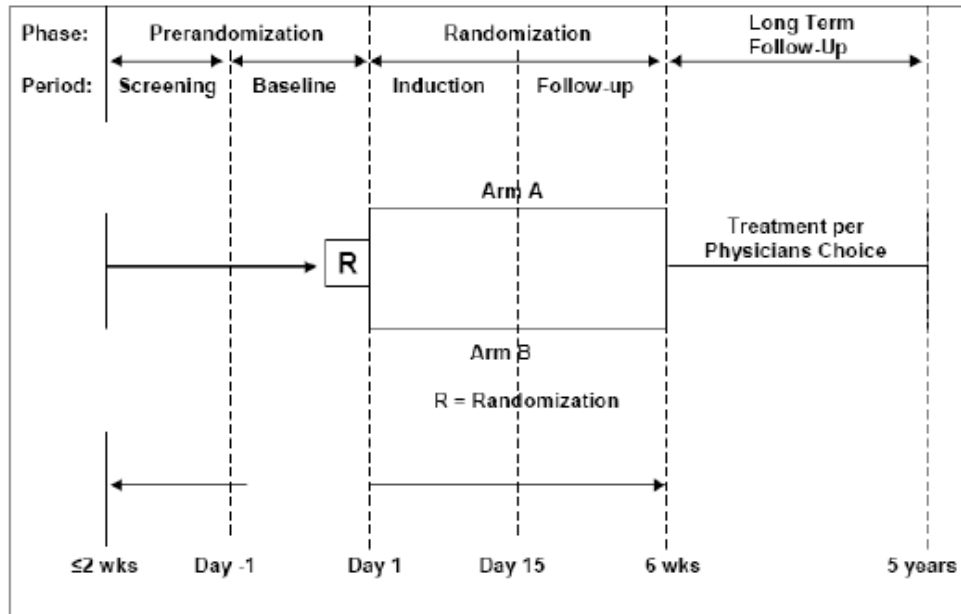
Figure 1   Three-Phase Study Design for Study DACO-202

25 subjects were enrolled in one of two arms in a 1:1 ratio:

- Arm A (investigational treatment): Subjects received decitabine priming for 5 days, followed by standard induction chemotherapy of daunorubicin, cytarabine, and etoposide for 10 days

- Arm B (control, reference treatment): Subjects received standard induction chemotherapy of daunorubicin, cytarabine, and etoposide for 10 days

The two treatment arms were stratified by age before randomization per ICH and FDA guidance: 1 to <2 years, 2 to 11 years, and 12 to 16 years.

Study population /Sample size

Study population

A total of 40 pediatric subjects with AML were selected across 22 sites. As of the final cut off date (19th July 2013), 25 subjects were enrolled at 11 sites and completed treatment.

Inclusion Criteria

1. Males and females, age 1 to 16 years, inclusive

2. Females of childbearing potential had to have a negative serum beta-human chorionic gonadotropin (β-hCG) at screening, a negative urine pregnancy test before starting study treatment, and agree to be abstinent or to use a highly effective method of contraceptionfor at least one menstrual cycle before starting study treatment and until 30 days after the last dose of study treatment.

3. Sexually mature male subjects who were not abstinent or had not undergone a successful vasectomy, and who were partners of females of childbearing potential had to use, or their partners had to use, a highly effective method of contraception starting for at least one menstrual cycle before starting study treatment and until at least 30 days after the last dose of study treatment.

4. Diagnosis of primary AML (bone marrow or peripheral blood blasts ≥20%)

5. Adequate cardiac function as defined by an echocardiogram or multiple-gated acquisition scan demonstrating an ejection fraction >50% or a shortening fraction >26%

6. Were willing and able to comply with all aspects of the protocol

7. Provided written informed consent from subject's guardian or legally authorized representative and child assent (if applicable)

Non-inclusion criteria

1. Females who were pregnant (positive β-hCG test) or lactating

2. History of chronic myelogenous leukemia [t(9;22)]

3. Diagnosis of acute promyelocytic leukemia (M3 subtype in French-American-British [FAB] classification)

4. Clinically symptomatic central nervous system (CNS) disease

5. AML associated with congenital syndromes such as Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, or Diamond-Blackfan anemia

6. White blood cell (WBC) count >100,000/mm3

7. Serum creatinine >2.5 mg/dL

8. Alanine aminotransferase (ALT) >5 x upper limit of normal (ULN), aspartate aminotransferase (AST) >5 x ULN, or total bilirubin >3 x ULN

9. Prior chemotherapy (other than hydroxyurea) or radiation therapy for AML

10. Known to have a positive test result for human immunodeficiency virus

11. Any past or current medical condition that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study

12. Was believed by the investigator to be medically unfit to receive the study treatment or unsuitable for any other reason

13. Was hypersensitive to decitabine, daunorubicin, cytarabine, or etoposide

14. Participated in a drug trial in the last 4 weeks

Sample Size
No statistical justification of the sample size was provided for this exploratory study. The statistical plan estimated that a sample size of 40 subjects would provide a reasonable estimate for the difference in CR rate between Arm A (Investigational Arm) and Arm B (Control Arm).

Treatments

Arm A Only:

• Decitabine 20 mg/m2 via 1-h intravenous (IV) infusion daily for 5 days (Days 1 to 5)

Arm A (after completion of decitabine) and Arm B (in sequential order of administration):

• Intrathecal cytarabine administered at the time of diagnostic lumbar puncture according to age-based dosing: 1 to <2 years, 30 mg; ≥2 to <3 years, 50 mg; ≥3 years, 70 mg

• Daunorubicin 50 mg/m2 (1.67 mg/kg if body surface area [BSA] <0.6 m2) 6-h IV infusion every other day over a 5-day period for a total of 3 infusions (Days 6, 8, 10 [Arm A] or Days 1, 3, 5 [Arm B])

• Cytarabine 100 mg/m2 (3.3 mg/kg if BSA <0.6 m2) slow IV push (over 15 minutes) every 12 h x 10 days (Days 6 to 15 [Arm A] or Days 1 to 10 [Arm B])

• Etoposide 100 mg/m2 (3.3 mg/kg if BSA <0.6 m2) 4-h IV infusion x 5 days (Days 6 to 10 [Arm A] or Days 1 to 5 [Arm B])

Duration of Treatment:

Arm A: 15 days (5 days' of decitabine plus 10 days' of induction chemotherapy)

Arm B: 10 days (induction chemotherapy only)

Outcomes/endpoints

Endpoints

Primary efficacy endpoint :

The primary efficacy parameter was the morphologic CR rate.

The criteria for determining disease response are detailed in the protocol and were based upon the criteria established by the International Working Group (IWG) in 2003. Definitions for the response categories are summarized as follows:

• Morphologic complete remission: Requires that the subject achieved a morphologic leukemia-free state and had an ANC >1000/μL and platelets >100,000/μL. Hemoglobin concentration or hematocrit had no bearing on remission status, although the patient had to be independent of transfusions.

• Morphologic complete remission with incomplete blood count recovery: Subjects who fulfilled all the criteria for CR except for residual neutropenia (<1000/μL) or thrombocytopenia (<100,000/μL).

• Partial remission (PR): Requires all hematologic values as for a CR, but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. A value of <5% blasts was also considered a PR if any blasts with Auer rods were present.

• Aplastic/hypoplastic marrow (leukemia not detected): Requires <5% blasts in the aspirate sample with marrow spicules, with a count of ≥200 nucleated cells. There was persistence of extramedullary disease; no blasts with Auer rods could be present.

• Leukemia not in remission or treatment failure: Subjects who achieved less than a PR.

• Recurrence or morphologic relapse: Defined as the reappearance of leukemic blasts in the peripheral blood or >5% blasts in the bone marrow not attributable to any other cause. The reappearance or development of cytologically proven extramedullary disease also indicated relapse.

The number and percentage of subjects who achieved a confirmed CR in each treatment arm were summarized, along with the corresponding 95% two-sided exact confidence interval (CI). Fisher's exact test was used for testing treatment effect. Complete remission was calculated for the FA population as the primary analysis. Complete remission was also calculated for the PP population.

Secondary efficacy endpoints :

- Time to CR

- Time to platelet recovery (≥ 100,000/mm3) and time to neutrophil recovery (absolute neutrophil count [ANC] ≥ 1000/mm3) after induction chemotherapy

- Minimal residual disease (MRD) following induction chemotherapy

- Leukemia-free survival (LFS) and overall survival (OS)

- DNA methylation following decitabine treatment

Pharmacokinetics and pharmarcodynamics

- Standard parameters of PK profile of decitabine in Arm A on Day 5 immediately before and at 30 minutes, 60 minutes (immediately before the end of infusion), 65, 90, 120 and 180 minutes after the infusion.

- Biomarkers of genome-wide patterns of DNA methylation

Safety endpoints:

- Extent of exposure

- AEs,

- Clinical laboratory evaluation

- Vital signs, physical findings and other safety measurements

Statistical Methods

Four populations were analyzed

Full Analysis (FA) Population included all subjects who received at least one dose of study treatment and who had at least one postdose efficacy measurement for response.

Per Protocol (PP) Population included subjects who sufficiently complied with the protocol.

Safety Population was the group of subjects who signed informed consent, received treatment, and had at least one postdose safety assessment.

Pharmacokinetic Population consisted of all patients who have at least one post-dose evaluable PK sample available.

> *CHMP assessment comment:*
>
> Global study design as well as inclusion and exclusion criteria are acceptable for this phase 2 exploratory study.

Results

Recruitment/ Number analysed

The final CSR contains efficacy, PK and safety data for all 25 subjects enrolled in the study as of the final clinical cutoff date of 19 Jul 2013.

A total of 98 patients with AML were screened for entry into the study. Of these 98 subjects, only 25 subjects were eligible and randomly assigned and treated at one of 11 sites in the US, Canada or Australia. Figure 2 presents the subject disposition for the FAS.
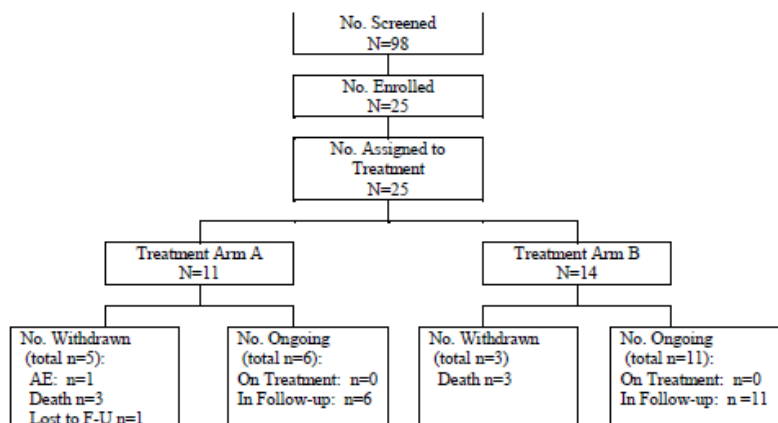
```
              No. Screened
                 N=98
                   │
              No. Enrolled
                 N=25
                   │
             No. Assigned to
                Treatment
                 N=25
          ┌────────┴────────┐
    Treatment Arm A    Treatment Arm B
        N=11               N=14
   ┌──────┴──────┐    ┌──────┴──────┐
No. Withdrawn  No. Ongoing  No. Withdrawn  No. Ongoing
(total n=5):   (total n=6):  (total n=3):  (total n=11):
AE: n=1        On Treatment: n=0  Death n=3  On Treatment: n=0
Death n=3      In Follow-up: n=6            In Follow-up: n=11
Lost to F-U n=1
```

Figure 2   Subject Disposition as of the Clinical Cutoff Date, Study DACO-202

The clinical cutoff date was 19 Jul 2013.
Treatment Arm A = decitabine + induction chemotherapy.
Treatment Arm B = induction chemotherapy alone.
All six deaths occurred > 30 days posttreatment.
Subject 10031003 in Arm A was lost to follow-up (F-U). At last contact, the subject was alive and in remission.
Source: Data Listings 16.2.1, 16.2.9, 16.2.16, 16.2.25.

A summary of the overall disposition of subjects in the Full Analysis Set (FAS) at Baseline is presented in Table 3. As of the clinical cutoff date, one subject (4%), assigned to Arm A, had discontinued treatment due to an AE. Six subjects had died, and one was lost to follow-up. The remaining 18 subjects completed treatment and were in survival follow-up.

Table 3   Subject Disposition and Early Termination Information, Full Analysis Set

Parameter Statistic	Arm A (Decitabine + Induction Chemotherapy)	Arm B (Induction Chemotherapy Alone)
Randomized, n (%)	11 (100)	14 (100)
Treated, n (%)	11 (100)	14 (100)
Completed Day 35 posttreatment visit, n (%)	10 (90.9)	14 (100)
Treatment ongoing, n (%)	0	0
Treatment discontinued, n (%)	1 (9.1)	0
Primary reason for discontinuation,[a] n (%)		
Adverse event[b]	1 (9.1)	0

CRF = case report form.
Percentages are based on the number of subjects randomly assigned and treated in the relevant treatment arm.
a: As reported on the Subject Disposition CRF.
b: Corresponding adverse events leading to discontinuation from the study/study treatment were reported on the Adverse Event CRF.
Source: Table 14.1.1 and Listing 16.2.1.   03SEP2013

No major violations occurred in this study. No subjects were excluded from the FAS, safety or PP populations.

Table 4   Analysis Populations, Study DACO-202

Analysis Set	Arm A Decitabine + Induction Chemotherapy n (%)	Arm B Induction Chemotherapy Alone n (%)
Full Analysis Set (FAS)[a]	11 (100)	14 (100)
Per Protocol (PP)[b]	11 (100)	14 (100)
Safety[c]	11 (100)	14 (100)
Pharmacokinetic (PK)[d]	11 (100)	0

FA = full analysis; PK = pharmacokinetics; PP = per protocol.
a: The full analysis set included all subjects who received at least one dose of study treatment and who had at least one postdose efficacy measurement for response.
b: The PP population included all subjects who sufficiently complied with the protocol.
c: The Safety population included all subjects who signed informed consent, received treatment, and had at least one postdose safety assessment.
d: The PK population included all subjects who had at least one evaluable postdose PK sample available.
Source: Table 14.1.2.   03SEP2013

CHMP assessment comment:

The study was overall well conducted; the dropout rate (4%, 1/25) is low. Forty subjects were planned for this study. However, the study was terminated prematurely after 25 subjects due to slow enrollment and the futility of observing a difference in remission rate between treatments arms following DSMB recommendation.

Baseline data

<u>Demographic and baseline characteristics:</u>

Table 5   Select Subject Demographics at Baseline, Full Analysis Set

Parameter Statistic	Arm A Decitabine + Induction Chemotherapy (N=11)	Arm B Induction Chemotherapy Alone (N=14)
Age, years		
Mean (SD)	8.7 (5.53)	8.6 (5.24)
Median	8.0	7.5
Min, Max	2, 16	1, 16
Age Category, n (%)		
1 to <2 years	0	1 (7.1)
2 to 11 years	7 (63.6)	8 (57.1)
12 to 16 years	4 (36.4)	5 (35.7)
Sex, n (%)		
Male	4 (36.4)	8 (57.1)
Female	7 (63.6)	6 (42.9)
Race, n (%)		
White	8 (72.7)	12 (85.7)
Black or African American	1 (9.1)	0
American Indian/Alaska Native	1 (9.1)	0
Asian	0	1 (7.1)
Other	1 (9.1)	1 (7.1)
Ethnicity, n (%)		
Hispanic or Latino	1 (9.1)	5 (35.7)
Not Hispanic or Latino	10 (90.9)	9 (64.3)
Weight, kg		
Mean (SD)	36.98 (22.745)	36.64 (26.478)
Median	24.60	27.40
Min, Max	10.1, 66.2	13.2, 108.3
Body Surface Area, m^2		
Mean (SD)	1.15 (0.509)	1.12 (0.516)
Median	0.92	0.99
Min, Max	0.5, 1.8	0.5, 2.3

Source: Tables 14.1.4 and 14.1.6.   03SEP2013

Overall, the median age of subjects were 8 years, 80% of them were white subjects. Only one subject in the 1 to 2-year age stratum was enrolled and assigned in the Arm B.

Baseline disease characteristics and cancer history:

All 25 subjects had confirmed de novo AML, a total of 21 subjects (84%) had >20% bone marrow blasts at baseline (Arm A: 9/11, 81.8% versus Arm B: 12/14 85.7%). The median time from diagnosis of AML to study entry was 2.0 days (range 0-4 days) and was the same for both arms. The most common FAB classification was M2 (8/25, 32%) which was more frequently in arm B than in arm A (n=6 42.9% versus n=2 18.2%).

Table 6   Baseline Disease Characteristics, Full Analysis Set

Parameter Statistic	Arm A Decitabine + Induction Chemotherapy (N=11)	Arm B Induction Chemotherapy Alone (N=14)
AML Type		
De novo AML[a] , n (%)	11 (100)	14 (100)
Time From Diagnosis of AML to Study Entry, days [b]		
Mean (SD)	1.6 (1.03)	1.6 (1.22)
Median	2.0	2.0
Min, Max	0, 4	0, 4
Blasts in Bone Marrow, %		
Category, n (%)		
≤ 20	1 (9.1)	2 (14.3)
> 20	9 (81.8)	12 (85.7)
Missing	1 (9.1)	0
n	10	14
Mean (SD)	56.5 (27.07)	53.9 (25.54)
Median	62.5	58.5
Min, Max	0, 84	16, 93
FAB Classification, n (%)		
M0	2 (18.2)	1 (7.1)
M1	2 (18.2)	0
M2	2 (18.2)	6 (42.9)
M4	3 (27.3)	2 (14.3)
M5	1 (9.1)	3 (21.4)
M7	0	2 (14.3)
Missing	1 (9.1)	0

AML = acute myeloid leukemia; FAB = French-American-British.
a: Based on pathology readings performed by the principal investigators.
b: Study entry = date informed consent was signed; may have coincided with the date of randomization.
Source: Table 14.1.5.   03SEP2013

CHMP assessment comment:

The demographic and baseline characteristics were globally well balanced between 2 arms in this small sample size study.

The use of prior medication including antineoplastic agents was similar between 2 arms.

Efficacy results

Primary efficacy results: Complete Remission rate

Table 8   Complete Remission Analysis at Visit 6, Full Analysis Set

Parameter	Arm A Decitabine + Induction Chemotherapy (N=11) n (%)	Arm A 95% CI	Arm B Induction Chemotherapy Alone (N=14) n (%)	Arm B 95% CI
Morphologic complete remission (CR)	3 (27.3)	(6.0, 61.0)	7 (50.0)	(23.0, 77.0)
Morphologic complete remission, with incomplete blood count recovery (CRi)	6 (54.5)	(23.4, 83.3)	5 (35.7)	(12.8, 64.9)
CR + CRi rate	9 (81.8)	(48.2, 97.7)	12 (85.7)	(57.2, 98.2)
Partial remission (PR)	0	(0, 28.5)	1 (7.1)	(0.2, 33.9)
Aplastic/hypoplastic marrow (leukemia not detected)[a]	0	(0, 28.5)	1 (7.1)	(0.2, 33.9)
Leukemia – not in remission[a]	1 (9.1)	(0.2, 41.3)	0	(0, 23.2)
Did not complete induction chemotherapy due to SAE [a]	1 (9.1)	(0.2, 41.3)	0	(0, 23.2)

CI = confidence interval; CR = complete remission, CRi = morphologic complete remission with incomplete blood count recovery; PR = partial remission, SAE = serious adverse event.
a: Nonresponder.
Source: Table 14.2.1.1.1 (13Aug2013).

Table 9   Complete Remission Rates at Visit 6 by Age Category, Full Analysis Set

Parameter	Arm A Decitabine + Induction Chemotherapy (N=11) n (%)	Arm A 95% CI	Arm B Induction Chemotherapy Alone (N=14) n (%)	Arm B 95% CI
Age 1 to < 2 years	n=0		n=1	
CR			1 (100.0)	(2.5, 100.0)
CR + CRi rate			1 (100.0)	(2.5, 100.0)
Age 2 to 11 years	n=7		n=8	
CR	2 (28.6)	(3.7, 71.0)	3 (37.5)	(8.5, 75.5)
CRi	4 (57.1)	(18.4, 90.1)	4 (50.0)	(15.7, 84.3)
CR + CRi rate	6 (85.7)	(42.1, 99.6)	7 (87.5)	(47.3, 99.7)
Age 12 to 16 years	n=4		n=5	
CR	1 (25.0)	(0.6, 80.6)	3 (60.0)	(14.7, 94.7)
CRi	2 (50.0)	(6.8, 93.2)	1 (20.0)	(0.5, 71.6)
CR + CRi rate	3 (75.0)	(19.4, 99.4)	4 (80.0)	(28.4, 99.5)

BM = bone marrow; CI = confidence interval; CR = Morphologic complete remission; CRi = Morphologic complete remission, with incomplete blood count recovery
Source: Table 14.2.1.1.4.

As shown in tables 8, 3 of the 11 subjects (27.3%) in Arm A and 7 of 14 subjects (50.0%) in Arm B achieved a CR in Study DACO-202. In Arm A, 1 subject did not achieve leukemic remission (ie, treatment failure), 1 subject did not complete induction chemotherapy due to a serious adverse event, and 6 subjects achieved a morphologic CR with incomplete blood count recovery (CRi). The total remission rate (CR+CRi) for Arm A was 81.8%. In Arm B, 1 subject had a partial response and 1 subject had aplastic marrow at the completion of induction chemotherapy; the total remission rate (CR+CRi) was 85.7%.

The response rates (CR+CRi) between Arms A and B were similar for both subjects age 2 to 11 years and subjects age 12 to 16 years. In Arm A, which included decitabine priming, the response rate (CR+CRi) was numerically higher among subjects in the younger age group (2 to 11 years; n=6/7, 85.7%) compared with those in the older age group (12 to 16 years; n=3/4, 75.0%). However, these results should be interpreted with caution due to the small number of subjects in each age group.

Myeloblast count: The median bone marrow myeloblast count at Baseline was 62.5% in Arm A and 58.5% in Arm B. Three weeks after the last dose of induction chemotherapy, median myeloblast counts were 1.5% and 1.0% in Arms A and B, respectively. This corresponds to a change from baseline of -52.4% and -55.0% for Arms A and B, respectively.

CHMP assessment comment:

Only one subject enrolled was younger than 2 years, analysis was limited to the 2 older age groups (2-11 and 12-16 years old).

The morphologic CR was lower in Arm A than in Arm B (3/11 27.3% versus 7/14, 50%). The total remission rate (CR+CRi) seems similar between two arms (81.8% in Arm A versus 85.7% in Arm B. In the Arm A, the response rate seems higher in subjects aged 2 to 11 years than older subjects aged 12 to 16 years (85.7% versus 75%).

The table 14.1.7.1 "Hematology at Baseline" showed that subjects in Arm A had lower baseline ANC value. Many of these subjects had delayed recovery in ANC counts. These differences were considered clinically relevant by the sponsor, and may have contributed to the lower CR rate and higher incidence of cytopenias (higher CRi) observed in Arm A as compared with Arm B. However due to the small

sample size in each group, these results should be interpreted with caution and no firm conclusion could be drawn from this study.

Secondary Efficacy endpoints:

Time to Complete remission

The median time to CR from the date of randomization was 43 days for subjects in Arm A and 37 days for subjects in Arm B. The median time to remission (CR+CRi) was 41 days for subjects in Arm A and 33 days for subjects in Arm B.
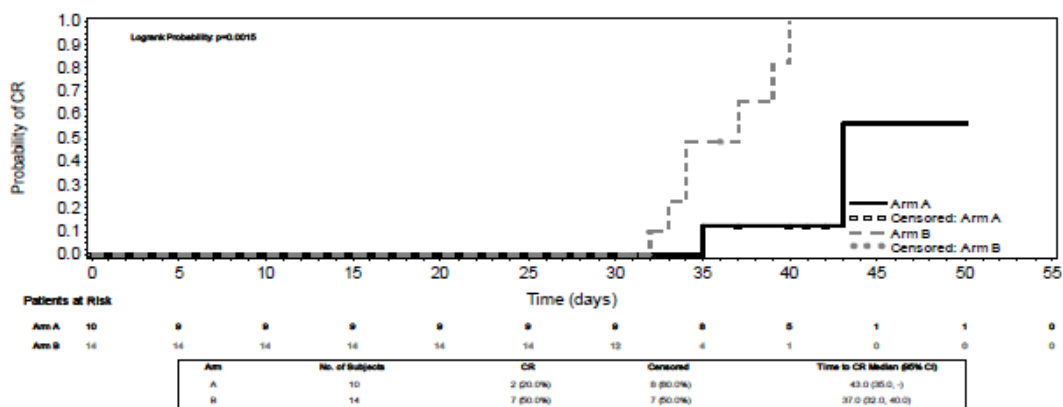

Figure 3   **Kaplan-Meier Plot of Time to Morphologic Complete Remission, Full Analysis Set**
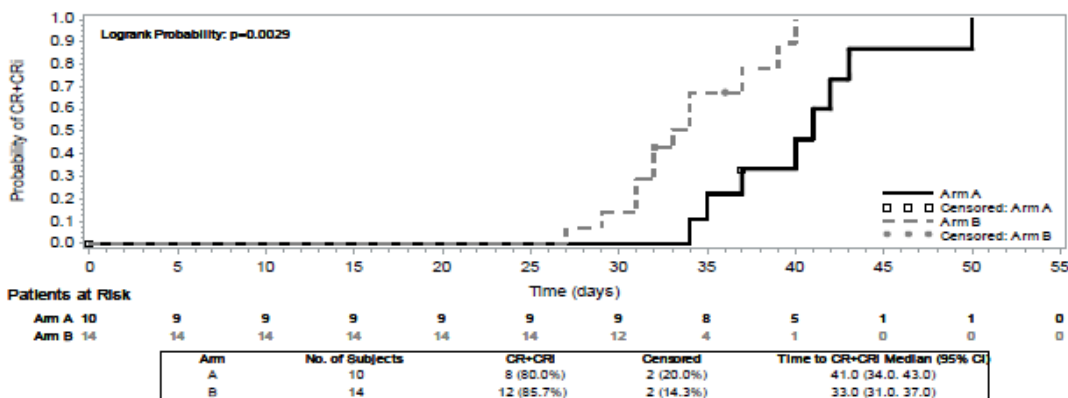
Source: Figure 14.2.2.

Figure 4   **Kaplan-Meier Plot of Time to CR + CRi, Full Analysis Set**

CI = confidence interval, CR = morphologic complete remission; CRi = morphologic complete remission with incomplete blood count recovery
Source: Figure 14.2.7.

CHMP assessment comment:

Clinical response was evaluated at the same time point (Visit 6, Day 35) during the study for 2 arms. Given the 5 days of decitabine treatment prior to the start of induction chemotherapy for subjects in Arm A, the median time to response between the treatment arms was comparable.

Time to neutrophil/platelet Recovery

Table 10   Kaplan-Meier Analysis of Times to Platelet and Neutrophil Recovery, Full Analysis Set

	Arm A	Arm B
	Decitabine + Induction Chemotherapy (N=11)	Induction Chemotherapy Alone (N=14)
Time to Platelet Recovery (to ≥ 100,000/mm³), days		
Number of subjects with recovery	11	14
Median (95% CI)	22.0 (6.0, 26.0)	14.5 (8.0, 18.0)
Min, Max[a]	2.0 – 31.0	2.0 – 24.0
1st quartile (95% CI)	21.0 (2.0, 22.0)	8.0 (2.0, 14.0)
3rd quartile (95% CI)	26.0 (21.0, 31.0)	18.0 (14.0, 24.0)
Time to Neutrophil Recovery (to ANC ≥ 1000/mm³), days		
Number of subjects with recovery	9	10
Number of subjects not recovered (censored)	2	4
Median (95% CI)	26.0 (13.0, 43.0)	18.0 (15.0, 25.0)
Min, Max[a]	2.0 – 43.0	8.0 – 39.0
1st quartile (95% CI)	20.0 (2.0, 26.0)	15.0 (8.0, 18.0)
3rd quartile (95% CI)	34.0 (21.0, 43.0)	25.0 (17.0, 39.0)

ANC = absolute neutrophil count; CI = confidence interval.
Median and first and third quartiles are based on Kaplan-Meier product-limit estimates.
a: censored value
Source: Table 14.2.2.4.

The median time to neutrophil recovery (ANC ≥1,000/mm3) from the date of randomization was longer for subjects in Arm A compared with subjects in Arm B (25 versus 18.0 days). The median time to platelet recovery (≥100,000/mm3) from the date of randomization was longer for subjects in Arm A compared with Arm B (22 versus 14.5 days).

CHMP assessment comment:

The median time to both neutrophil and platelet recovery was approximately 8 days longer for subjects in Arm A than in Arm B. These differences in recovery time may be in part due to the additional 5 days of decitabine treatment for subjects in Arm A, which would appear to delay recovery time when measured at a fixed timepoint (Visit 6 for all subjects).

It is important to note that subjects may have received platelet transfusion and the baseline ANC value were lower in Arm A, which could also affect time to counts.

Here again, these results should be interpreted with caution due to small size of subjects in each arm.

Minimum residual disease analyses

Table 12   Subject Listing for Status of Minimum Residual Disease by Time Point, Full Analysis Set

Subject ID	Baseline	End of Treatment
Treatment Arm A		
1003-1003	10%	0%
1003-1006		
1003-1008		
1006-1001	8%	0%
1006-1002	1%	0%
1006-1003	76%	0%
1006-1004[a]	20%	15%
1006-1005		
1015-1001	32%	0.1%
1018-1001[b]	NA	NA
1104-1001	NA	0%
Treatment Arm B		
1001-1001		
1002-1001	NA	0%
1003-1001	NA	NA
1003-1002	NA	NA
1003-1004	NA	0%
1003-1005		
1003-1007		
1010-1001	NA	0%
1016-1001	NA	NA
1023-1001	NA	0.4%
1101-1001	NA	0%
1101-1002		
1104-1002	NA	NA
1104-1003		

CR = morphologic complete remission; CRi = morphologic complete remission with incomplete count recovery; MRD = minimal residual disease; NA = not available: sample not processed due to lack of viability, degradation, or was outside established time frame for processing; SAE = serious adverse event.
a: Subject did not attain CR or CRi during the study.
b: Subject discontinued treatment due to an SAE and was not evaluated for MRD at the end of treatment.
Source: Preliminary report from Fred Hutchinson Cancer Research Center.

CHMP assessment comment:

Only six subjects assigned to treatment Arm A had viable MRD measurement at baseline and at end-of-treatment. No subjects in Arm B had viable sample. Five of 6 subjects in Arm A were MRD+ at baseline and showed MRD levels below the threshold of detection at end-of-treatment. All of these subjects achieved a morphological CR. None of comparative conclusion between 2 arms can be drawn from these results.

Leukemia-free survival and Overall Survival

As of the clinical cutoff date, 6 subjects had died (3 subjects each in arm), all more than 30 days posttreatment; 18 subjects were still alive (1 subject who had achieved a CR at Visit 6 had relapse of leukemia and was still alive).

Table 11   Listing of Subjects Who Died, Full Analysis Set

Subject ID	Response at Visit 6	Date of EOT (Study Day)[a]	Date of Relapse	Date of Death	Duration between EOT and Death (days)[b]
Arm A					
1006-1001	CRi	23Jun2011 (45)	NR	13Dec2011	173
1006-1003	CRi	20Oct2011 (43)	NR	29Mar2012	161
1006-1004[c]	Leukemia - not in remission	08Nov2011 (43)	06Feb2012	13Jul2012	248
Arm B					
1003-1005	PR	NR	NR	29Oct2012	NR
1010-1001	CR	12Sep2011 (43)	23Mar2012	01Jan2013	477
1023-1001	CR	28Nov2011 (33)	04Sep2012	26Sep2012	303

CR = morphologic complete remission; CRi = morphologic complete remission with incomplete count recovery; EOT = end of treatment; IT = intrathecal; IV = intravenous; NR = none recorded; PR = partial response; SAE = serious adverse event.
a: All six subjects completed assigned study treatment.
b: All deaths occurred more than 30 days posttreatment.
c: Subject did not attain CR or CRi during the study. Subject received posttreatment antineoplastic therapy with Induction II high-dose IV cytarabine, IV mitoxantrone and IT cytarabine starting 08Nov2011 and attained remission on 30Nov2011, 22 days poststudy treatment.
Source: Listings 16.2.1, 16.2.15, 16.2.16, and 16.2.26.

> *CHMP assessment comment:*
>
> There were insufficient data as of the clinical cutoff date to perform an analysis of LFS. Median OS could not be estimated.

Pharmacokinetics

Plasma concentration of decitabine were quantifiable in all 11 decitabine-treated subjects up to the last time point of 180 minutes. Selected PK parameters of decitabine in overall pediatric subjects and by age group are shown in Table 13. Mean plasma concentration-time profile on linear scale is presented in Figure 5.

Table 13   Mean Pharmacokinetic Parameters of decitabine on day 5 of Treatment – Overall and by Age group

Pharmacokinetic Parameter	Age Group (y)				Arm A Total (N=11)	
	2 - 11 (N=7)		12 - 16 (N=4)			
	Mean Value	CV%	Mean Value	CV%	Mean Value	CV%
C_{max} (ng/mL)	286 (131)	45.88	307 (36.9)	12.02	294 (104)	35.48
t_{max} (h)	0.803 (0.272)	33.93	0.88 (0.243)	27.66	0.831 (0.253)	30.40
$t_{1/2}$ (h)	0.458 (0.0777)	16.96	0.446 (0.0967)	21.70	0.453 (0.0804)	17.73
AUC_{0-t} (ng•h/mL)	211 (90.0)	42.58	218 (35.1)	16.09	214 (72.4)	33.85
$AUC_{0-\infty}$ (ng•h/mL)	212 (90.0)	42.39	219 (35.7)	16.28	215 (72.5)	33.74
CL (L/h)	110 (113)	103.36	161 (23.9)	14.90	128 (92.3)	72.09
Vd_{ss} (L)	40.7 (52.0)	127.74	54.1 (9.67)	17.88	45.5 (41.1)	90.35

AUC = area under the concentration-time curve; CL = total body clearance; C_{max} = maximum concentration; CV = coefficient of variance; NR = not reported; $t_{1/2}$ = half-life; t_{max} = time to C_{max}; Vd_{ss} = volume of distribution at steady-state concentrations.
All values presented as mean ± SD.
Source: Table 14.2.2.3.2
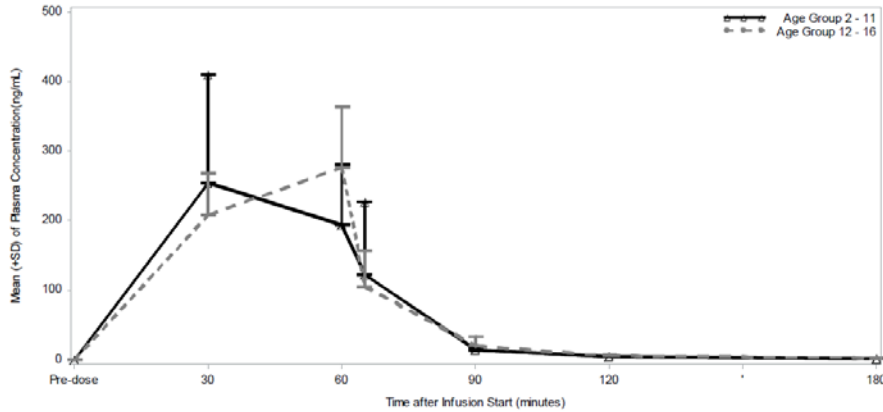
Postinfusion, plasma concentrations declined in a bi-exponential manner.

Mean (SD) PK values for the 11 decitabine-treated subjects were: Cmax, 294 (104) ng/mL; AUC0-∞, 215 (72.5) ng·h/mL; CL, 128 (92.3) L/h; Vdss, 45.5 (41.1) L; t½, 0.453 (0.0804) h; tmax, 0.831 h (0.253).

CHMP assessment comment:

Intersubject variability in PK values was higher than expected, but did not appear to be age related given the limited number of subjects.

Pharmacodynamics

Results for pharmacodynamics assessments such as DNA methylation, biomarker identification, mRNA expression, clonogenic assay are not found in this CSR.

CHMP assessment comment

Efficacy summary based on the efficacy results from 25 pediatric subjects (n=11 in Arm A and n=14 in Arm B):

There were no apparent differences in remission rates (CR+CRi) between subjects in Arm A who received decitabine priming, and subjects in Arm B, who received only induction chemotherapy. Response rates (CR+CRi) as of the Visit 6 timepoint (3 weeks post-chemiotherapy) were similar between treatment arms (81.8% [n=9/11] for Arm A and 85.7% [n=12/14]) for Arm B). However, a numerically higher CR rate was noted in Arm B (Arm A, 27.3%; Arm B, 50.0%). The significantly lower baseline ANC values in Arm A could partially contribute to the lower CR rate and higher incidence of CRi in Arm A.

Median times to ANC and platelet recovery appeared to be approximately 8 days longer in Arm A than Arm B. These differences in recovery time may be in part due to the additional 5 days of decitabine treatment for subjects in Arm A, which would appear to delay recovery time when measured at a fixed timepoint (Visit 6 for all subjects).

Seven subjects had leukemic relapse or death at the clinical cutoff date; there was no relevant difference between the 2 treatment arms.

Intersubject variability in PK values was higher than expected, but did not appear to be age related given the limited number of subjects.

Overall efficacy results should be interpreted with caution due to small size of subjects in each arm.

Safety results

All subjects in Arm A completed 1 cycle of 5-Day decitabine treatment; no subjects treated with decitabine had a dose modification.

The number of chemotherapy infusions and median relative dose intensities for each chemotherapeutic agent were similar between the treatment arms, except for cytarabine. Subjects in Arm B received on average 1 day more of treatment with cytarabine, with a dose intensity approximately 83 mg/m2/week higher, compared with subjects in Arm A. These results appear to be due to the results of 1 subject in Arm A, who received only 1 dose of cytarabine.

Treatment-emergent Adverse Events

All 25 subjects had at least 1 TEAE.

No. (%) of subjects with:	Arm A Decitabine + Induction Chemotherapy (N=11)	Arm B Induction Chemotherapy Alone (N=14)
Any grade TEAE	11 (100)	14 (100)
Treatment-related TEAEs	8 (72.7)	NA
Grade 3-4 TEAEs	11 (100)[a]	12 (85.7)
Serious AEs	2 (18.2)	1 (7.1)
Deaths		
During treatment or within 30 days posttreatment	0	0
> 30 days posttreatment	3 (27.3%)[b]	3 (21.4%)
TEAE leading to treatment discontinuation	1 (9.1)	0
Treatment-related toxicity (TRT)	1 (9.1)[a]	NA

NA = not applicable; TEAE = treatment-emergent adverse event; TRT = treatment-related toxicity.
TRT only assessed for decitabine.
a: TRT in Arm A was defined as a nonresolving Grade 3 or 4 nonhematologic or hematologic toxicity, or time to platelet recovery ($\geq$ 100,000/mm^3) and neutrophil recovery ($\geq$ 1000/mm^3) that continued beyond 55 days following the last day of induction chemotherapy, in the absence of leukemia.
b: 1 subject (1006-1004) did not attain remission during the treatment period of the study. Source: Tables 14.3.1 and 14.3.2.

The most frequently reported TEAEs, occurring in 50% or more of subjects overall, were vomiting (n=15/ [60%]); anemia, decreased appetite, diarrhea, and white blood cell count decreased, each of which occurred in 14 of the 25 subjects (56.0%); and nausea (n=13/25, 52%). These TEAEs were consistent with the subjects' underlying AML diagnosis and the known safety profiles of study treatment.

Treatment-emergent AEs that occurred in at least four more subjects in Arm A (decitabine) than in Arm B included decreased appetite (Arm A, n=9 [81.8%]; Arm B n=5 [35.7%]), constipation (Arm A, n=7 [63.6%]; Arm B, n=2 [14.3%]), hypotension (Arm A, n=7 [63.6%]; Arm B, n=1 [7.1%]), catheter site erythema (Arm A, n=6 [54.5%]; Arm B, n=2, [14.3%]), and catheter site hemorrhage (Arm A, n=3 [27.3%]; Arm B, n=0).
Adverse events that occurred in at least three more subjects in Arm B than in Arm A (in decreasing order of frequency) were febrile neutropenia (57.1% vs. 27.3%), weight decreased (35.7% vs. 27.3%), epistaxis (35.7% vs. 9.1%), neutrophil count decreased (35.7% vs. 0), oropharyngeal pain (28.6% vs. 9.1%), and ear pain (21.4% vs. 0).

Eight subjects (72.7%) had a TEAE reported as related to decitabine by the investigator. Causal relationship was not captured for the chemotherapy alone.

Table 19   Treatment-Related Adverse Events in Two or More Subjects in Arm A by System Organ Class and Preferred Term, Safety Population

MedDRA SOC Preferred Term	Arm A Decitabine + Induction Chemotherapy (N=11)
Total n (%) of subjects with related TEAE	8 (72.7)
Blood and Lymphatic System Disorders	**7 (63.6)**
Anemia	5 (45.5)
Neutropenia	2 (18.2)
Thrombocytopenia	4 (36.4)
Gastrointestinal Disorders	**6 (54.5)**
Constipation	2 (18.2)
Nausea	3 (27.3)
Vomiting	2 (18.2)
General Disorders and Administration Site Conditions	**2 (18.2)**
Pyrexia	2 (18.2)
Investigations	**6 (54.5)**
Platelet count decreased	3 (27.3)
White blood cell count decreased	5 (45.5)
Skin and Subcutaneous Tissue Disorders	**4 (36.4)**
Alopecia	2 (18.2)
Petechiae	2 (18.2)
Rash	2 (18.2)

MedDRA version 14.0.
MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event.
Source: Table 14.3.5.1.

Treatment-Related Toxicity

One decitabine-treated subject had a treatment-related toxicity (TRT). Subject 1015-1001 had Grade 3 decreased WBC (protocol-defined TRT) on Day 7 and Grade 3 anemia on Day 24. Both events were reported by the investigator to be possibly related to decitabine. However, neither event was reported as serious and no action was taken. The subject had not recovered at the time this CSR was prepared.

Grade 3-4 Adverse Events

All but 2 subjects had at least 1 Grade 3-4 TEAE: 11/11 in arm A, 12/14 in arm B.
The most frequently reported Grade 3-4 AEs, occurring in 25% or more of subjects overall, were anaemia (n=14/25, 56.0%), white blood cell count decreased (n=14/25, 56.0%), febrile neutropenia (n=11/25, 44.0%), platelet count decreased (n=10/25, 40.0%), and thrombocytopenia (n=8/25, 32.0%). These TEAEs are all consistent with the subjects' underlying disease or the known safety profile of study treatment.
Severe TEAEs that occurred in at least three more subjects in Arm A than in Arm B were hypokalaemia (36.4% vs. 7.1%) and decreased appetite (27.3% vs. 0). Severe TEAEs that occurred in at least three more subjects in Arm B than in Arm A were febrile neutropenia (57.1% vs. 27.3%), neutrophil count decreased (35.7% vs. 0), and stomatitis (21.4% vs. 0).
No Grade 5 events occurred in this study.

Serious Adverse Events

Two subjects in Arm A had serious TEAEs. One subject had 2 SAEs (appendicitis and large intestine perforation) on Study Day 6 that led to treatment discontinuation. The second subject had lower gastrointestinal haemorrhage. One subject in Arm B had an SAE of sepsis on Day 35, after completing

the course of study treatment. The investigator rated the event as moderate and the subject recovered. None of the SAES were reported by the investigator as being related to study treatment.
There were no AEs that led to decitabine dose modification (interruption/delay/reduction).

None of the 11 subjects in Arm A had a decitabine dose modification.
One subject (1018-1001) had two SAEs, appendicitis and large intestine perforation, which led to treatment discontinuation on Study Day 6. There were no AEs that led to dose modification.

Deaths

There were no induction-related deaths. No deaths occurred during the treatment period or within 30 days after last dose. However, six deaths did occur posttreatment, 3 in each arm.

Table 21   Causes and Timing of Posttreatment Deaths, Full Analysis Set

Subject ID	Cause of Death	Duration between EOT and Death (days)[a]
Arm A		
1006-1001	Pseudomonal sepsis, necrotic bowel, multisystem organ failure	173
1006-1003	multiorgan failure, complications of BMT	161
1006-1004	side effects from additional anticancer treatment	248
Arm B		
1003-1005	progressive disease	NR
1010-1001	progressive disease	477
1023-1001	multiorgan system failure, relapsed AML, sepsis	303

AML = acute myelogenous leukemia, BMT = bone marrow transplant; EOT = end of treatment, NR = not recorded.
All six subjects completed their assigned study treatment.
a: All deaths occurred more than 30 days posttreatment.
Source: Listings 16.2.1, 16.2.15, 16.2.16, and 16.2.26.

All six deaths occurred more than 30 days after the subjects' last dose of study treatment. There did not appear to be any differences between treatment arms in either the timing or causes of death.

For two subjects, death was attributed to progressive disease (i.e., AML). Two deaths were attributed to "other" reasons, namely multiorgan system failure. One subject died of complications due to bone marrow transplant approximately 7 months after EOT of this study. The sixth subject (1006-1004) died of an adverse drug reaction (ADR) to additional anticancer treatment approximately 8 months after EOT.

Clinical Laboratory Evaluation

Of note, two subjects in Arm A did not have baseline lab values recorded. Subjects in Arm A had lower mean and median ANC values, and lower mean platelet count, compared with those in Arm B at Baseline. Furthermore, while minimum ANC and platelet count values were similar between treatment arms, Arm B had much higher maximum values. Median baseline chemistry laboratory values were similar between treatment arms in the FAS.

Table 22   Selected Disease-Related Hematology Values at Baseline, Full Analysis Set

Laboratory Parameter (unit)	Arm A Decitabine + Induction Chemotherapy	Arm B Induction Chemotherapy Alone
ANC (GI/L)	n=9	n=14
Mean (SD)	0.739 (1.4120)	3.774 (3.8498)
Median	0.280	2.820
Min, max	0.04, 4.46	0.02, 14.05
Hemoglobin (g/L)	n=9	n=14
Mean (SD)	90.1 (10.41)	93.3 (11.11)
Median	92.0	95.0
Min, max	75, 104	73, 108
Lymphocytes (GI/L)	n=9	n=14
Mean (SD)	5.908 (6.9845)	6.380 (8.1758)
Median	2.130	2.545
Min, max	0.81, 21.17	0.91, 30.85
Platelet count (GI/L)	n=9	n=13
Mean (SD)	76.9 (26.39)	89.8 (66.38)
Median	71.0	64.0
Min, max	34, 112	20, 266

ANC = absolute neutrophil count; max = maximum; min = minimum.
Baseline laboratory values were not recorded for 2 subjects in Arm A; AML diagnosis was made based on actual pathology reading.
Source: Table 14.1.7.1.   03SEP2013

Postbaseline Changes in Laboratory Values: Mean serum chemistry values appeared to fluctuate or increase over time in both treatment arms. In general, Arm A had higher mean alkaline phosphatase values at most time points. Mean creatinine levels increased over the course of the study in Arm A, but not in Arm B. No other meaningful changes were observed (including potassium).

Hematology: Grade 3-4 baseline hematologic values were similar between treatment arms, except for ANC. Eight subjects (72.7%) in Arm A compared with four subjects (28.6%) in Arm B had Grade 3-4 ANC values at Baseline, consistent with the known variability in disease severity.

Shifts from normal (Grade 0) or Grade 1 at Baseline to either Grade 3 or 4 during treatment were observed more frequently in Arm B than in Arm A for hemoglobin (Arm A: n=1/9, 11.1%; Arm B: n=3/14, 21.4%), lymphocytes (Arm A: n=1/9, 11.1%; Arm B: n=8/14, 57.1%), ANC (Arm A: n=1/9, 11.1%; Arm B: n=9/14, 64.3%), and leukocytes (Arm A: n=5/9, 55.6%; Arm B: n=11/14, 78.6%). The intergroup differences in shifts in lymphocyte, leukocyte, and ANC values may be clinically meaningful, however, the number of subjects is small.

Table 24   Total Incidence of Subjects With Grade 3-4 Hematologic Laboratory Values at Baseline or During Treatment, Safety Population

Laboratory Parameter	Arm A Decitabine + Induction Chemotherapy (N=11) Baseline[a]	Arm A During Treatment[b]	Arm B Induction Chemotherapy Alone (N=14) Baseline[a]	Arm B During Treatment[b]
	n (%) of subjects with Grade 3-4 value at:			
Anemia	2 (18.2)	5 (45.5)	2 (14.3)	6 (42.9)
Neutropenia	8 (72.7)	10 (90.9)	4 (28.6)	14 (100)
Thrombocytopenia	2 (18.2)	9 (81.8)	3 (21.4)	13 (92.9)
WBC	3 (27.3)	10 (90.9)	2 (14.3)	14 (100)

Anemia = hemoglobin; CTCAE = Common Terminology Criteria for Adverse Events; neutropenia = absolute neutrophil count; thrombocytopenia = platelets; WBC = white blood cell count.
Percentages are based on total number of subjects in each group as the denominator.
a: Total number of subjects with CTCAE Grade 3 or 4 value at Baseline.
b: Total number of subjects with worst CTCAE Grade 3 or 4 value during treatment or at follow-up Weeks 1, 2, and 3 after chemotherapy.
Source: Table 14.3.7.8.

All subjects in the Safety population with baseline data had at least one postbaseline hematologic laboratory abnormality that was rated Grade 3 or 4. However, none were deemed serious or led to discontinuation of treatment. The incidence of Grade 3-4 lymphocyte count was higher in Arm B (n=8, 88.9%) than in Arm A (n=1, 14.3%). No other clinically meaningful intergroup differences were observed for total incidence of Grade 3-4 hematologic laboratory abnormalities.

One subject in Arm A had protocol-defined treatment-related toxicity, namely Grade 3 decreased WBC. Profound neutropenia and thrombocytopenia are expected events during induction chemotherapy.

Table 26   Incidence of Worst Grade 3 or 4 Values During Treatment for CTCAE-Coded Laboratory Parameters, Safety Population

Laboratory Parameter[a] Postbaseline Grade	Arm A Decitabine + Induction Chemotherapy (N=11) 3	Arm A 4	Arm B Induction Chemotherapy Alone (N=14) 3	Arm B 4
	n (%) of subjects with:			
Hematology	n=9[b]		n=14	
Absolute neutrophil count	0	9 (100)	0	14 (100)
Hemoglobin	5 (55.6)	0	6 (42.9)	0
Leukocytes	1 (11.1)	8 (88.9)	0	14 (100)
Lymphocytes	1 (11.1)	0	7 (50.0)	1 (7.1)
Platelets	0	8 (88.9)	1 (7.7)	11 (84.6)
Serum Chemistry	n=11		n=14	
ALT	0	0	1 (7.1)	1 (7.1)
AST	0	0	1 (7.1)	0
Glucose	0	0	2 (14.3)	0
Potassium	1 (9.1)	1 (9.1)	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Percentages based on total number of subjects with both nonmissing baseline and postbaseline values.
a: Only laboratory parameters with Grade 3-4 postbaseline values are displayed.
b: Two subjects in Arm A had missing baseline hematology values; therefore, the denominator is based on 9 subjects.
Source: Tables 14.3.7.5 and 14.3.7.6.

Serum Chemistry: One subject in Arm A had a Grade 4 potassium value at Baseline, which was also Grade 4 during decitabine treatment, but resolved to Grade 0 on Day 6. One subject in Arm B had a Grade 3 glucose value at Baseline, which was also Grade 3 on Day 2 and Visit 6, but Grade 0 or 1 at all other time points during treatment, including the end-of-treatment visit.

No other Grade 3-4 values for serum chemistry parameters were observed at Baseline. Shifts from normal (Grade 0) or Grade 1 at Baseline to either Grade 3 or 4 during treatment were observed for ALT (Arm A: n=0; Arm B: n=2), AST (Arm A: n=0; Arm B: n=1), glucose (Arm A: n=0; Arm B: n=1), and potassium (Arm A: n=1; Arm B: n=0). There did not appear to be any meaningful differences between treatment arms.

A total of 8 subjects (Arm A: n=5/11, 45.4%; Arm B: n=3/14 21.4%) had one or more postbaseline Grade 3-4 serum chemistry values. The most frequently occurring serum chemistry abnormality was low potassium. Overall, 10 subjects (Arm A: n=7/11, 63.6%; Arm B: n=3/14, 21.4%) had low (Grade 1-4) postbaseline potassium values. These were Grade 3-4 in seven subjects (28%) overall, and the incidence was higher in Arm A than in Arm B (Arm A: n=6/11, 54.5%; Arm B: n=1/14, 7.1%). These findings are consistent with sequelae of chemotherapy as well as those previously observed with decitabine in adult subjects with AML (Study DACO-016; where 13.8% vs. 8.2% of subjects in the decitabine and TC arms, respectively, had a shift in potassium level from Grade 0-2 at Baseline to Grade 3-4 during treatment).

Grade 3-4 low potassium values were the most frequently reported serum chemistry abnormalities. Hypokalemia was monitored by the sponsor throughout the study, and were presented to the DSMB following discussions with the principal investigators. Hypokalemia was most likely due to GI disturbances and electrolyte imbalances from chemotherapy-induced vomiting; all cases were manageable with supportive care, such as potassium supplementation or parenteral nutrition.

No Grade 3-4 changes in bilirubin or creatinine were reported.

Vital signs

There were no meaningful differences in mean or median values between treatment arms for any vital sign parameter. No significant trends were noted in mean blood pressure, pulse, respiration rate, weight, or body temperature from Baseline over time for either of the treatment arms.

Vital sign findings were considered by the sponsor to be clinically significant if they were severe (Grade 3 or 4), reported as serious, or led to treatment discontinuation. Overall, vital sign parameters were reported as a TEAE as follows: pyrexia (n=8), hypotension (including the preferred term 'orthostatic hypotension') (n=8) and hypertension (n=3). All of these were mild or moderate, except for one subject in Arm A who had multiple episodes of Grade 3 hypotension and one subject in Arm B who had Grade 3 pyrexia. Changes in blood pressure were reported as TEAEs by the investigator more frequently in Arm A than in Arm B.

Electrocardiogram Data

Electrocardiograms were not performed routinely per protocol in this study. However, some cardiac TEAEs were recorded. Tachycardia and sinus tachycardia were reported more frequently in Arm A (n=6, 54.5%) compared with Arm B (n=2, 14.3%). All of the recorded events were rated Grade 1 or "mild" except for one subject in Arm A who had Grade 3 tachycardia on Study Day 16 in association with Grade 3 febrile neutropenia (onset Day 15), Grade 3 hypotension (onset Day 16), and serious Grade 3 lower gastrointestinal haemorrhage (onset Day 16). The subject recovered from all of the events, which the investigator reported as being not related to study treatment.

CHMP assessment comment

All patients in both treatment arms presented at least 1 TEAE.

AE reported in at least 50 % of the patients, both treatment arms included, are in line with the known safety profile of decitabine and associated chemotherapy (cytarabine, daunorubicine, etoposide).

Safety profiles appeared similar in both arms, despite higher incidence of severe hypokalaemia (36.4% vs. 7.1%) and decreased appetite (27.3% vs. 0) in decitabine arm.

All subjects had at least 1 Grade 3-4 TEAE in arm A, and 85% of the patients in arm B.

There was no treatment-related death.

3 patients presented serious AE, none assessed as treatment related:

- 2 in arm A: 1 patient with appendicitis and large intestine perforation, leading to chemotherapy interruption, and & patient with gastrointestinal haemorrhage.

- 1 in arm B: sepsis at D35.

Clinical Laboratory Evaluation, vital signs and electrocardiogramms did not raise safety signal in decitabine arm in paediatric population.

Based on data provided, no safety signal was raised and reported AE are in line with the known safety profile of decitabine.

2.3.3. Discussion on clinical aspects

The results from the Study Daco-202, a Phase 2 multicenter study of decitabine epigenetic priming prior to induction chemotherapy versus chemotherapy alone in children with AML showed:

- There were no apparent differences in remission rates (CR+CRi) between subjects in Arm A who received decitabine priming and subjects in Arm B, who received only induction chemotherapy. However, a numerically higher CR rate was noted in Arm B (Arm A, 27.3%; Arm B 50.0%).

- Median times to ANC and platelet recovery appeared to be approximately 8 days longer in Arm A than Arm B. This longer time to blood count recovery may be due at least in part to the additional 5 days of decitabine treatment in Arm A.

  The significantly lower baseline ANC values in Arm A may also contribute to the lower CR rate and longer recovery time in Arm A.

- The incidence of remission failure at Visit 6 was similar between the two treatment arms.

- Seven subjects had leukemic relapse or death at the clinical cutoff date; there was no relevant difference between the two treatment arms.

- High intersubject variability in decitabine PK parameters was observed; however, there did not appear to be an age-related trend among the limited number of subjects.

- Safety profiles appeared similar in both arms, despite higher incidence of severe hypokalaemia (36.4% vs. 7.1%) and decreased appetite (27.3% vs. 0) in decitabine arm.

- There were no induction-related deaths

- No safety signal was raised and reported AE are in line with the known safety profile of decitabine.

3. CHMP's overall conclusion and recommendation

The addition of decitabine pretreatment had no effect on clinical response rates or MRD results when compared with chemotherapy alone. The increased time to response and time to blood cell count recovery for subjects pretreated with decitabine was likely the result of the additional 5-day period before induction chemotherapy was started for subjects in decitabine Arm A.

No safety signal was raised and reported AE are in line with the known safety profile of decitabine.

Overall, it is agreed with the MAH that the data from Study E7373-G000-202 alone do not influence the benefit-risk balance and therfore no SPC changes are deemed necessary for Dacogen at this time.

X Fulfilled:

No regulatory action required.

☐ **Not fulfilled:**