Janssen Korea Ltd.

Clinical Study Report

A Prospective, Multicenter, Observational Study of Dacogen Treatment in Patients with Myelodysplastic Syndrome

DECKOR5002

Clinical Study Protocol DEC-KOR-5002; Observational study

Dacogen (decitabine)

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: 김석란 MD

DATE STUDY INITIATED: 4 December 2008

DATE STUDY COMPLETED: 29 September 2010

Issue Date: 9 August 2012
Prepared by: Janssen Korea Ltd.
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GCP Compliance: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

SYNOPSIS

Issue Date: 2 August 2012

Name of Sponsor/Company	Janssen Korea Ltd.
Name of Finished Product	Dacogen
Name of Active Ingredient	Decitabine

Protocol Number: DEC-KOR-5002

Title of Study: A Prospective, Multicenter, Observational Study of Dacogen Treatment in Patients with Myelodysplastic Syndrome

Study Name: DIVA

NCT No.: NCT01041846

[Principal] Investigator: Je Hwan Lee, MD,PhD, Ulsan University Asan Medical Center

Study Centers: A total of 24 institutions participated in the clinical study, including the followings:

Name of Institution
1. Gyeongsang National University Hospital
2. Korea University Guro Hospital
3. Korea University Anam Hospital
4. Kosin University Hospital
5. Gil Hospital
6. Daegu Catholic Hospital
7. Dong-A University Medical Center
8. Veteran's Hospital
9. Busan Paik Hospital
10. Soonchunhyang University Bucheon Hospital
11. Seoul National University Bundang Hospital
12. Samsung Medical Center
13. Seoul National University Hospital
14. Asan Medical Center
15. Shinchon Severance Hospital
16. Ajou University Hospital
17. Yeungnam University Hospital
18. Ewha University Mokdong Hospital
19. Inha University Hospital
20. Chonbuk National University Hospital
21. Chungang University Hospital
22. Chungbuk National University Hospital
23. Hallym University Pyeongchon Hospital
24. Chonnam National University Hwasun Hospital

Publication (Reference): A prospective multicenter observational study of decitabine treatment in Korean patients with myelodysplastic syndrome. Haematologica. 2011 Oct;96(10):1441-7

Study Period: It was conducted from 4 December 2008 to 29 September 2010.

Objectives: The objective of the clinical study was to evaluate efficacy and safety in patients treated with Dacogen™ Injection (hereinafter referred to as "Dacogen"), and the primary efficacy endpoint was overall response rate (CR+PR+HI). The major secondary objectives were to evaluate safety by examining adverse events and to evaluate efficacy by analyzing cytogenetic response and survival (Overall survival (OS), Time to AML evolution (TTA), and Progression free survival (PFS)).

Methodology: The clinical study was a prospective, open, multicenter, single-arm, observational study. Blood cell count in peripheral blood was measured in the beginning of each treatment cycle and was repeated as needed if clinically meaningful, and bone marrow examination data was collected 2 cycles and 4 cycles after administering the study drug. Additionally, cytogenetic response rate (if available), transfusion dependency by patient (the applicable date in order to figure out the number of days independent from transfusion), and the number of days in hospitalization (reason for hospitalization) were observed. Safety was evaluated based on adverse event monitoring, physical examination, and clinical laboratory tests (hematology and clinical chemistry).

Number of Subjects: The total sample size planned in this clinical study was 92 subjects.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Male or female patients in 20 years of age or older.
- Patients diagnosed of myelodysplastic syndrome (MDS, primary or secondary); including 야 함; chronic myelomonocytic leukemia (CMML)
- Patients with IPSS Int-1 or higher
- Hypomethylating agent naïve patients
- In case of women, postmenopausal women, or patients who underwent sterilization or were sexually not active; and in case of women of childbearing potential, patients were required to use an effective contraceptive method (e.g., oral contraceptive prescription, contraceptive injection, interuterine device, double barrier method, contraceptive patch, or sterilization of a male partner) before participating the study and during the study.
- In case of men, patients who were not planned to have child within 2 months of completing Dacogen treatment.
- Subjects should understand the study objectives and required procedures and should sign on the informed consent form indicating the voluntary willingness to participate in the study.

Exclusion Criteria:

- Patients diagnosed of acute myeloid leukemia (AML, more than 20% of myeloblast) or other malignant advanced disease.
- Patients infected by active virus or bacteria.
- Patients who had been treated with Vidaza™ or Dacogen previously
- Patients having hypersensitivity to an excipient of Dacogen
- Pregnant or lactating women

- Patients having a psychotic disease which might interfere with cooperation of treatment and monitoring condition of the clinical trial.

Duration of Treatment: Duration of treatment in this clinical trial was at least 4 cycles, and the final evaluation was conducted after 8 weeks (Day 56-61) while the follow-up observation was done at least for 8 weeks after the last dose of study drug.

Criteria for Evaluation:

Efficacy Evaluation:

Based on the IWG 2006 Response Criteria, overall response rate, hematological improvement, cytogenetic response rate (if available), amount of transfusion requirement, and the number of days in hospitalization were observed.

Complete Response (CR); should be maintained at least for 4 weeks.

- Bone marrow: ≤5% myeloblast (normal differentiation from all cell lines)
- Continuous dysplasia could be observed.
- Peripheral blood

  - Hemoglobin > 11g/dL (not transfused, excluding erythropoietin)

  - Neurophils ≥ 1500/mm^3 (excluding bone marrow growth factor)

  - Thrombocytes ≥ 100,000/mm^3 (excluding platelet promoting growth factor)

  - Blast cells - 0%

Partial Response (PR); should be maintained at least for 4 weeks.

- With the following exceptions, all of the evaluation criteria for complete response above should be satisfied.
- Compared to pre-treatment, myeloblasts decreased by 50% or more but still exceeding 5%.
- Cellularity and type were not relevant.

Safety Evaluation:

Physical examination and hematology and clinical chemistry tests were performed on Day 1 of each cycle prior to the administration of study drug and in the treatment closing visit performed 56~61 days after administering the last dose of study drug. If clinically necessary, hematology and clinical chemistry tests were repeated. Safety evaluation was conducted based on adverse event reporting during the treatment after the subject informed consent and during the period for 56 days (8 weeks) after administering the last dose of study drug which was until the treatment closing visit. Intensity and severity of adverse events were evaluated by using the general adverse event category (CTCAE) Version 3.0 by National Cancer Institute (NCI). All adverse events were recorded in the case report form (CRF). Clinically relevant changes in clinical laboratory tests and physical examination were recorded as adverse events. Serious adverse events were reported as soon as they became aware of, by using the form provided by the sponsor.

Statistical Methods:

Sample Size Determination:

In this study, the number of patients were calculated so that efficacy could be hypothesized based on the degree of improvement (%) in overall response rate following Dacogen administration. The followings were hypothesized in order to calculate the effective number of patients:

1. Level of significance α=0.05
2. Based on the existing study results, the percentage of improvement was hypothesized at 35%.
3. Accuracy of the percentage of improvement was determined based on the length of interval estimation in the percentage of improvement after the study, and it was based on 11% because there was no case previously used which could be applied to this study.

Assuming the numbers 1~3 above, the number of patients required for this study was as follows:

$$N = \left[\frac{Z_{1-\alpha/2}\sqrt{P(1-p)}}{L}\right]^2 \fallingdotseq 73$$

- P=0.35
- $Z_{1-\alpha/2} = 1.96$ level of significance 5% (two-side test)
- L=0.11

  N=92 (assuming 20% of drop-out rate)

Analysis Population Criteria:

The analysis of results in this study was performed for the full analysis set (FAS). The FAS analysis population was defined as the population excluding subjects who violated the inclusion or exclusion criteria or those who had not received the study drug at all among the entire subject group. In case of a missing value for the major endpoint, it was handled by using the method of Last Observation Carried forward (LOCF) which replaced the missing value with the data obtained most recently from time when the missing value was produced.

In addition, among the subjects who participated in the study, 'Per-Protocol Analysis' (hereinafter referred to as PP analysis population) in which the analysis was targeted to subjects who completed the study without violating the protocol was additionally performed. At this time, the target to be included in the PP analysis population was the subjects who had the relevant CRF data available for all days of evaluation.

Results:

Study Population:

A total of 103 subjects participated in the clinical study, and among them, 38 subjects (36.89%) discontinued the clinical study. The most dominant reason for the withdrawal from the study was failure/progression in 13 subjects (36.89%), followed by withdrawal of informed consent in 6 subjects (5.83%), allogeneic HCT in 5 subjects (4.85%), toxicities, financial issue, and follow-up loss in 4 subjects (3.88%) respectively, and life-threatening fungal pneumonia and no efficacy in one subject (0.97%), respectively. 65 subjects completed the clinical study until the end.

For the cases violating the study protocol while implementing the clinical study, there were a total of 2 subjects who violated the inclusion criteria, among those who participated the clinical study.

Among 103 subjects of the entire enrollment, all of 103 subjects received the study drug at least once and were included in the safety analysis population; 101 subjects excluding 2 subjects who violated the

inclusion or exclusion criteria were included in the FAS (Full analysis set); and 63 subjects were included for efficacy analysis as the PP (Per protocol) set which the subjects completed the study without violating the protocol.

Efficacy Results:

In terms of response rate following the study drug treatment in this study, complete response (CR) was shown in 3 subjects (2.97%), partial response in one subject (0.99%), and hematologic improvement (Marrow CR+HI, Marrow CR-HI, HI) in 51 subjects (50.50%). That is, 55 subjects showed response by treatment, indicating response rate at 54.46% with 95% Clopper-Pearson confidence interval at 44.24%~64.40%.

Response rate (FAS)

Response	N	(%)	95% Confidence interval*
Improvement in hematopoiesis	55	(54.46%)	44.24%~64.40%
CR	3	(2.97%)	-
PR	1	(0.99%)	-
Marrow CR + HI	21	(20.79%)	-
Marrow CR – HI	8	(7.92%)	-
HI	22	(21.78%)	-
SD	12	(11.88%)	-
Failure	6	(5.94%)	-
NE	28	(25.72%)	-

*Clopper-Pearson Confidence Interval

The results for the secondary efficacy endpoints including cytogenetic response rate, Overall survival, Time to AML and Progression-free survival were as follows.

In terms of distribution of cytogenetic response after the study drug treatment, complete response (CR) was seen in 5 subjects (4.95%) and partial response (PR) in 2 subjects (1.98%) but not evaluable was shown in 82 subjects (82.18%). Among all 101 subjects, improvement in genetic response rate was 6.93% in 7 subjects, with 95% Clopper-Pearson confidence interval at 2.83%~13.76%.

Cytogenetic response rate (FAS)

Response	N	(%)	95% Confidence interval*
Genetic improvement (all subjects)	7	(6.93%)	2.83%~13.76%
Genetic improvement (excluding subjects not evaluable)	7	(38.89%)	17.30%~64.26%
CR	5	(4.95%)	-
PR	2	(1.98%)	-
NR	11	(10.89%)	-
Not evaluable	83	(82.18%)	-

The median duration of survival estimated from overall survival was calculated in 541 days, with 95% confidence interval at 507-575 days. For the result of time to AML, the median of AML occurrence could not be calculated, but the incidence rate of AML at Year 1 was 18.50%. Finally for the results of progression-free survival, the median progression-free survival in the FAS population was 527 days with 95% confidence interval at 431-601 days.

Survival Data Analysis (FAS)

Item	N	Censored n	Event n	Median [Days]	95 % CI [Days]
Overall survival	101	58	43	541	(507, 575)
Time to AML	101	83	18	NA	NA
Progression-free survival	101	59	42	527	(431, 601)

Safety Results: Among all 103 subjects who participated in the clinical study and received the study drug at least once, a total of 94 subjects (91.26%) experienced 663 cases of adverse events, with the reported death cases in 19 subjects, and 49 subjects (47.57%) experienced 160 cases of adverse drug reactions. 134 cases of serious adverse events were reported in 63 subjects (61.17%), and among them, 50 cases were reported as those related to the drug.

Summary of Adverse Events

	Number of Subjects	Incidence Rate N (%)	Number of Cases N
Adverse Events	94	91.26%	663
Adverse Drug Reactions	49	47.57%	160
Serious Adverse Events	63	61.17%	134
Serious Adverse Events Related to the Drug	30	29.15%	50
Death	19	18.45%	21

Among the adverse events which occurred during the clinical study, those indicating high incidence rate were presented in the table below, including febrile neurtropenia which was the most dominant as 33 cases occurring in 25 subjects (24.27%), followed by pyrexia, neutropenia, dyspnea, pneumonia, and headache.

Adverse Events with High Incidence Rate

Type of Adverse Events	Adverse Events			Adverse Drug Reactions		
	Incidence Rate		Number of Cases	Incidence Rate		Number of Cases
	N	(%)	N	N	(%)	N
Total	**94**	**(91.26%)**	**663**	**49**	**(47.57%)**	**160**
Febrile neutropenia	25	(24.27%)	33	16	(15.53%)	22
Pyrexia	24	(23.30%)	40	5	(4.85%)	6
Neutropenia	22	(21.36%)	43	14	(13.59%)	23
Dyspnoea	18	(17.48%)	26	1	(0.97%)	1
Pneumonia	17	(16.50%)	18	5	(4.85%)	5
Headache	16	(15.53%)	17	0	(0.00%)	0

Study Limitation: This study was an observational study so there is limitation that the study was conducted under general environment of treatment; therefore, efficacy could not be confirmed based on the study, but the study showed efficacy exceeding the expected response rate in spite of indicating conservative response rate.

Additionally when evaluating response rate, there were many subjects not evaluable, from which conservative response rate was presented, but it is thought that this needed to be considered.

Conclusions: This study had the objectives to collect Korean data about efficacy and safety for 5-day therapy of Dacogen in patients with myelodysplastic syndrome. Compared to the hypothesis based on the existing study result (35% of response improvement rate), the study showed 54.45% of high response rate. Based on the results, it could be concluded that 5-day therapy of Dacogen increased treatment effect in patients with myelodysplastic syndrome.

Dacogen treatment in Korean patients with myelodysplastic syndrome was effective, and the reported adverse events were mostly predictable based on the existing study results.