Janssen Korea Ltd.

Clinical Study Report

비-자가조혈모세포 이식 대상으로 진단 후 초기에 보르테조밉으로 치료 받은 다발성 골수종 환자의 삶의 질 관찰 연구

A prospective, open-label, multicenter observational study to evaluate the QoL of non-transplant candidate multiple myeloma patients treated with the early bortezomib

Clinical Study Protocol BOR-KOR-5022; Observational Study

Bortezomib

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: 김석란 MD

DATE STUDY INITIATED: 5 October 2009

DATE STUDY COMPELTED: 19 July 2011

Issue Date: 28 September 2012
Prepared by: Janssen Korea Ltd.
[Document No.: Insert Number (eg,: EDMS-XXX-########:1.0)]

GCP Compliance: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

SYNOPSIS

Issue Date: 4 September 2012

Name of Sponsor/Company	Janssen Korea Ltd.
Name of Finished Product	Velcade Injection
Name of Active Ingredient	Bortezomib

Protocol Number: BOR-KOR-5022

Title of Study: A prospective, open-label, multicenter observational study to evaluate the QoL of non-transplant candidate multiple myeloma patients treated with the early bortezomib

Study Name: QuBig

NCT Number: NCT01060202

Clinical Registry No.: CR016750

[Coordinating] Investigator: Chulwon Suh M.D., Ph.D. – Study Center/Asan Medical Center, 388-1 Pungnap-2-dong, Songpa-gu, Seoul

Study Centers: A total of 19 institutions participated in the clinical study, including the followings.

Name of Center
1. Catholic University St. Mary's Hospital
2. Gyeongsang National University Hospital
3. Korea University Guro Hospital
4. Korea University Anam Hospital
5. Kosin University Hospital
6. Daegu Catholic University Hospital
7. Dong-A University Hospital
8. Samsung Medical Center
9. Asan Medical Center
10. St. Vincent Hospital
11. Sooncheonhyang University Bucheon Hospital
12. Korea Cancer Center
13. Ewha University Mokdong Hospital
14. Inje University Paik Hospital
15. Inha University Hospital
16. Chonbuk National University Hospital
17. Chungbuk National University Hospital
18. Hallym University Sacred Heart Hospital (Pyeongchon)
19. Chonnam National University Hwasun Hospital

Publication (Reference): There is none published yet from the clinical study.

Study Period: It was conducted from 5 October 2009 to 19 July 2011.

Objectives:

This study was conducted to evaluate quality of life of patients with multiple myeloma who failed in the first-line treatment initially following the diagnosis (defined as less than PR) and changed their medication to bortezomib combination chemotherapy. The primary objective was to measure the quality of life (EORTC QLQ-C30+EQ 5D).

The major secondary objectives of this study were to investigate correlation between quality of life of the primary objective and the parameter such as complete response, overall response (CR+VGPR+PR), time to response (TTR), survival (progression free survival (PFS), overall survival (OS) and to evaluate safety.

Methodology and Number of Subjects: The clinical study was a prospective, open, multicenter, single-arm observational study to observe quality of life in patients with multiple myeloma before and after treatment with bortezomib using EORTC QLQ-C30 and EQ-3D, and the total sample size planned included 116 subjects.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Male or female subjects in 20 years of age or older,
- Patients not in subject of HDT/SCT for the following reasons:
  - Patients in 65 years of age or older,
  - If younger than 65 years old, patients having significant complications which might have negative impact on HDT/SCT tolerability.
- Subjects classified as high risk patients,
- Subjects with symptomatic multiple myeloma
  - ≥ 10% of monoclonal plasma cells in bone marrow and/or histologically proven plasmacytoma,
  - Presence of monoclonal protein in serum and/or urine: Serum M-protein (> 1g/dL) or urine M-protein (> 200mg/dL),
  - Organ dysfunction related to myeloma (at least one):
    [C] Hypercalcemia (serum calcium > 10.5mg/L, or if higher than normal level)
    [R] Renal insufficiency (serum creatinine > 2mg/dL)
    [A] Anemia (hemoglobin < 10g/dL or 2g < normal level)
    [B] Bone lytic lesion or osteoporosis
- Presence of disease measurable based on the following definitions: In case of secretory type multiple myeloma, the measureable disease was defined by all measurable serum monoclonal protein levels (IgG or IgM M-protein > 1g/dL, IgA M-protein > 0.5g/dL, IgD M-protein > 0.05g/dL, or 200mg/24 hours or longer of light-chain secretion).
- For small amount secretory or non-secretory multiple myeloma, abnormal FLC ratio should be confirmed.
  - Serum FLC assay: Involved FLC level ≥ 10mg/dL with abnormal serum FLC ratio
- Patients with less than PR following the initial treatment,
- Patients with the initial treatment duration for 6 months or shorter,
- Patients who were able to complete the patient questionnaire,
- Female subjects should be in menopause, have been sterilized, or be abstained from sexual activities, and females of childbearing potential should use an effective contraceptive method (eg, prescription of oral contraceptive medication, injectable contraceptives, intrauterine device, double barrier

method, contraceptive patch, and sterilization of the male partner) prior to and during the clinical study.
- Subjects should sign the informed consent form specifying that they have understood the objectives and procedures required and participated in the clinical study voluntarily.

Exclusion Criteria:

- Patients diagnosed of asymptomatic multiple myeloma or MGUS. Asymptomatic multiple myeloma was defined as asymptomatic multiple myeloma without presence of bone lytic lesion. MGUS was defined as the presence of serum monoclonal protein less than 3g/dL; absence of renal insufficiency related to monoclonal protein, bone lytic lesion, anemia and hypercalcemia (if measured), and plasma cell ratio in bone marrow less than 10%,
- Subjects previously treated with bortezomib,
- Patients having hypersensitivity with this drug and its ingredients or having its history,
- Subjects with severe peripheral neuropathy (Neuropathy ≥ Grade 2 based on the NCI CTC version 3.0)
- Pregnant or lactating women,
- Subjects who had had mental illness which might have interfere with cooperation in treatment and monitoring condition of the clinical study

Duration of Treatment: This study was an observational study, which was conducted under the condition of routine medical practice.

Subjects received bortezomib monotherapy or combination therapy with bortezomib, and all subjects participating in the study received treatment with bortezomib at least for 4 cycles.

The recommended dose of this drug was intravenous bolus injection for 3-5 seconds of 1.3mg/m^2 single dose twice a week (on Day 1, 4, 8 and 11) for 2 weeks, followed by 10 days (from Day 12 to Day 21) of resting period, resulting in one treatment cycle of total 3 weeksl.

Criteria for Evaluation:

Efficacy Evaluation:

In order to evaluate quality of life, EORTC QLQ-C30 and EQ-5D patient questionnaires were used.

- For continuous variables for changes in quality of life (EORTC QLQ-C30 and EQ-5D) of the primary efficacy endpoint, Wilcoxon signed rank-sum test was performed.

- For correlation between the measurement of quality of life (EORTC QLQ-C30 + EQ-5D) of the primary efficacy endpoint and each parameter such as complete response, overall response (CR+VGPR+PR), time to response (TTR), or survival (progression free survival, Wilcoxon rank-sum test was performed. In addition, Cox proportional hazards model was performed for difference in changes by item of EORTC QLQ-C30 and EQ-5D based on time to response before and after treatment with bortezomib.

Safety Evaluation:

Safety data were collected based on adverse events reported from the start of the clinical study (subject informed consent), during the treatment, and during the period of 30 days after last dose of the study drug,

which was until the treatment closure visit. Intensity and severity of adverse events were evaluated by using National Cancer Institute (NCI) Common Terminology Criteria of Adverse Events (CTCAE) 3.0 Version. All adverse events were recorded in the case report form (CRF). Clinically meaningful changes in clinical laboratory tests and physical examination were documented as adverse events. Serious adverse events were to be reported using the form provided by the sponsor as soon as investigators became aware of them.

Statistical Methods:

Sample Size Determination:

Primary efficacy endpoint of the clinical study was defined as the percentage of change in Global health status/quality of life score before administration of bortezomib, the study drug, and at final evaluation. Approximately 10% of improvement in the score could be seen as clinically meaningful, and the number of patients was calculated by hypothesizing that the percentage of patients with 10% or more of improvement in health status/quality of life was 70%.

In order to calculate the effective number of patients, the followings were hypothesized.

1. Significance level α=0.05
2. The percentage of patients with 10% or more of improvement in health staus/quality of life was hypothesized at 70%.
3. Accuracy of the patient percentage was based on 20% when considering full population of patients with multiple myeloma annually accrued and the duration of the clinical study.

When hypothesizing the above 1~3, the number of patients required for this clinical study was as follows:

$$N = \left[\frac{Z_{1-\alpha/2}\sqrt{P(1-p)}}{L}\right]^2 \fallingdotseq 81$$

- P=0.7
- $Z_{1-\alpha/2} = 1.96$, significance level 5 % (two-sided test)
- L=0.2
  N=116 (assuming 30% of dropout rate)

Analysis Population Criteria:

Subjects who had taken the study drug at least once were in subject of evaluation.

Results:

Study Population:

A total of 61 subjects were enrolled in the clinical study, and among them, 32 subjects (52.46%) completed the clinical study. The most dominant reason for withdrawal was adverse events and death occurring in 10 subjects (16.39%), followed by withdrawal of informed consent in 5 subjects (8.20 %), loss of follow-up (including no visit) and study termination by investigators in 3 subjects (4.92%), respectively, completion of treatment for complete response and disease progression in 2 subjects (3.28%),

respectively, and others in 4 subjects (6.56%). There were three cases of violating the study protocol in this clinical study, which were all violation of the inclusion criteria.

All enrolled subjects received the study drug at least once and were included in the safety population. 58 subjects excluding 3 subjects who violated the inclusion/exclusion criteria were included in the FAS (Full Analysis Set) population, and 22 subjects from the PP (Per Protocol) set excluding those who completed the treatment at less than Cycle 4 were included in the efficacy analysis.

Analysis Data Sets

	N	(%)
Subjects enrolled in the clinical study	61	
FAS (Full analysis set)	58	(95.08 %)
PP (Per-protocol)	32	(52.46 %)
Safety analysis set	61	(100.00 %)

Efficacy Results:

As a result of measurement in EORTC QLQ-C30 before and after treatment with bortezomib in this study, change in Global health status/QoL at the end point compared to baseline was -7.05±25.18, indicating that Global health status and quality of life were deteriorated and the change was indicated as statistically significant difference (p=0.0403). In addition, change in the functional scales was shown to be declined by -26.71±36.78 and -24.36±32.63 at the end point compared to baseline for emotional and cognitive function, respectively, indicating statistically significant difference (p<0.0001 and p<0.0001, respectively). Change in the symptom scales/items was indicated increased by 5.98±32.33 and 8.55±28.32 from baseline to the end point for dyspnea and diarrhea, respectively, with statistically significant difference (p=0.0100 and p=0.0081, respectively). Finally, change in the financial difficulties was shown to be improved by -3.42±34.02, but showing no statistically significant difference (p=0.3004).

Changes in EORTC QLQ-C30 (FAS)

Type	Change*	N			p-value†
Global health status/QoL	**Global health status/QoL**	39	Mean ± SD Median Min-Max	-7.05 ± 25.18 -8.33 -91.67 ~ 66.67	0.0403
Functional scales	**Physical functioning**	39	Mean ± SD Median Min-Max	-5.64 ± 29.04 -6.67 -93.33 ~ 53.33	0.2984
	Role functioning	39	Mean ± SD Median Min-Max	-10.26 ± 38.16 0.00 -100.00 ~ 66.67	0.1807
	Emotional functioning	39	Mean ± SD Median Min-Max	-26.71 ± 36.78 -25.00 -100.00 ~ 33.33	<.0001
	Cognitive functioning	39	Mean ± SD Median Min-Max	-24.36 ± 32.63 -16.67 -100.00 ~ 33.33	<.0001
	Social functioning	39	Mean ± SD	0.43 ± 32.55	1.0000

Type	Change*	N			p-value†
			Median	0.00	
			Min-Max	-66.67 ~ 66.67	
			Mean ± SD	-0.57 ± 34.00	
	Fatigue	39	Median	0.00	0.9390
			Min-Max	-66.67 ~ 66.67	
			Mean ± SD	3.42 ± 21.35	
	Nausea and vomiting	39	Median	0.00	0.1779
			Min-Max	-50.00 ~ 50.00	
			Mean ± SD	5.98 ± 35.76	
	Pain	39	Median	0.00	0.3575
			Min-Max	-66.67 ~ 83.33	
			Mean ± SD	5.98 ± 32.33	
	Dyspnoea	39	Median	0.00	0.0100
Symptom scales/items			Min-Max	-66.67 ~ 66.67	
			Mean ± SD	6.84 ± 36.01	
	Insomnia	39	Median	0.00	0.1954
			Min-Max	-66.67 ~ 100.00	
			Mean ± SD	0.00 ± 41.89	
	Appetite loss	39	Median	0.00	0.9165
			Min-Max	-100.00 ~ 100.00	
			Mean ± SD	3.42 ± 21.35	
	Constipation	39	Median	0.00	0.2156
			Min-Max	-66.67 ~ 33.33	
			Mean ± SD	8.55 ± 28.32	
	Diarrhoea	39	Median	0.00	0.0081
			Min-Max	-66.67 ~ 66.67	
			Mean ± SD	-3.42 ± 34.02	
Financial difficulties	**Financial difficulties**	39	Median	0.00	0.3004
			Min-Max	-100.00 ~ 66.67	

* Change = (End of Treatment phase) - (Baseline)

† Wilcoxon Signed –Rank Test

For the measurement of EQ-5D before and after treatment with bortezomib in this study, change in the EQ-5D Index from baseline to the end point was shown with the health status somewhat aggravated by -0.010±0.284, but indicating no statistical significance (p=0.4445). Next, change in the EQ-5D VAS from baseline to the end point was shown with the health status somewhat aggrevated by -3.87±22.15, but indicating no statistical significance (p=0.1827).

Changes in EQ –5D (FAS)

	N			p-value†
		Mean ± SD	-0.010 ± 0.284	
EQ-5D Index Change*	39	Median	-0.008	0.4445
		Min-Max	-0.691 ~ 0.894	
		Mean ± SD	-3.87 ± 22.15	
EQ-5D VAS Change*	39	Median	-5.00	0.1827
		Min-Max	-50.00 ~ 60.00	

* Change = (End of Treatment phase) - (Baseline)

† Wilcoxon Signed –Rank Test

Safety Results: Among total 61 subjects who had participated in the clinical study and taken the study drug at least once, 278 adverse events occurred in a total of 47 subjects (77.05 %), with 7 subjects reporting death cases, and 109 adverse drug reactions occurred in 32 subjects (52.46 %). 47 serious adverse events were examined in 22 subjects (36.07 %), and 16 events of them were reported as related to the study drug.

Summary of Adverse Events

	Number of Subjects	Incidence Rate N (%)	Number of Events N
Adverse events	47	77.05%	278
Adverse drug reactions	32	52.46%	109
Serious adverse events	22	36.07%	47
Serious adverse events related to study drug	11	18.03%	16
Death	7	11.48%	8*

* Two adverse events in one subject were reported to cause death.

Among the adverse events reported from the clinical study, adverse events showing at least 5% of incidence rate are shown in **Table 34**, including 30 cases of neuropathy peripheral most commonly occurring in 17 subjects (27.87 %), followed by 18 cases of thrombocytopenia in 12 subjects (19.67 %), 13 cases of pneumonia in 11 subjects (18.03 %), and 16 cases of diarrhea in 10 subjects (16.39 %).

Adverse Events Showing At Least 5% of Incidence Rate

Type of Adverse Events	Adverse Events		
	Incidence Rate		Number of Events
	N	(%)	N
Neuropathy peripheral	17	(27.87%)	30
Thrombocytopenia	12	(19.67%)	18
Pneumonia	11	(18.03%)	13
Diarrhoea	10	(16.39%)	16
Asthenia	9	(14.75%)	14
Constipation	8	(13.11%)	9
Pyrexia	7	(11.48%)	7
Anaemia	6	(9.84%)	10
Decreased appetite	6	(9.84%)	8
Fatigue	6	(9.84%)	8
Back pain	6	(9.84%)	6
Neutropenia	6	(9.84%)	6
Abdominal pain	4	(6.56%)	6
Cough	4	(6.56%)	6
Dizziness	4	(6.56%)	5
Dyspnoea	4	(6.56%)	5
Face oedema	4	(6.56%)	4
Herpes zoster	4	(6.56%)	4
Insomnia	4	(6.56%)	4
Upper respiratory tract infection	4	(6.56%)	4

Study Limitations: There is limitation to evaluate Global health status and quality of life for treatment with bortezomib clinically since the number of subjects enrolled in this study was smaller than the planned sample size and many patients were terminated early from the study.

Conclusions: This study was to measure quality of life in non-transplant candidate patients with multiple myeloma who failed in the first-line treatment initially following the diagnosis and changed their medication to bortezomib combination chemotherapy, but on the contrary to what was planned, it was indicated in the FAS that Global health status and quality of life were somewhat deteriorated after the treatment compared to pre-treatment.

Nevertheless, there is limitation to evaluate Global health status and quality of life for treatment with bortezomib clinically since the number of subjects enrolled in this study was smaller than the planned sample size and many patients were terminated early from the study.