SYNOPSIS

Issue Date:

Name of Sponsor/Company	Xian-Janssen Pharmaceutical, Ltd
Name of Finished Product	Velcade®
Name of Active Ingredient(s)	JNJ-26866138 (bortezomib)

Protocol No.: 26866138MMY4031 (VEL-CHN-MA-01)

Title of Study: VELCADE® (Bortezomib for Injection) Observational Study

NCT No.: NCT01675245

Clinical Registry No.: CR006373

Principal Investigator(s): Dr. Shen Zhixiang, MD - Shanghai Jiaotong University affiliated Ruijin Hospital

Study Center(s): This study was conducted at 43 centers (sites) in China.

Publication (Reference): None.

Study Period: First subject enrolled on 17 March 2006 and last subject completed the last visit on 31 May 2010. Database lock occurred on 17 January 2011.

Phase of Development: 4

Objectives: This observational study was conducted to document VELCADE® (bortezomib) utilization in subjects who initiated VELCADE therapy for the approved indication in a naturalistic setting.

Prospective data were collected and analyzed in "real-world" medical practice regarding the following clinical outcomes associated with the use of VELCADE:

Primary Objectives:

- VELCADE usage: indication, treatment sequence (lines of therapy), dosage, course and combined chemotherapy
- VELCADE treatment results:
  - Efficacy: disease response/progression, time to response/ progression, duration of response and survival
  - Safety: Adverse events (AEs).

Methodology:

This was a national, multi-center, non-interventional, observational study to collect information on the practical utilization and safety in Chinese multiple myeloma (MM) subjects treated with VELCADE. VELCADE was to be used in subjects who received 1 or more prior treatments and experienced disease progression in the most recent treatment.

The study consisted of 3 phases, including, screening phase, treatment phase, and follow-up phase. In the screening phase, data were to be collected on the basis of subject's demographic status, components of disease severity assessment, and potential prognostic factors. Data on prior cancer treatments were to be collected retrospectively at baseline for subjects receiving cancer treatment prior to receiving VELCADE. In the treatment phase, VELCADE was to be administered intravenously for a 2-week treatment period followed by a 10-day rest period. Each treatment cycle consisted of 21 days. Prospective observational data were to be collected during treatment with VELCADE. Data collection was to occur at baseline and at the end of each treatment cycle of VELCADE up to 8 treatment cycles via electronic data capture with the exception of serious adverse event (SAE) reporting. The SAE reporting was to be done within 24 hours of knowledge of the event to the assigned local operating company designate. After the 8 cycles' treatment phase, subjects were to be followed every 12 weeks for up to 3 years (prospectively from the date of the subject's initiation of VELCADE) to document long-term survival data. During

this phase, subsequent treatment and therapies (including initiation date and end date, and best response) for MM, survival, and future disease progression were to be collected. For subjects who reinitiated VELCADE, data collection had to follow VELCADE treatment period documentation process.

Number of Subjects (planned and analyzed): Planned-Recurrent and refractory MM subjects in real-world practice were planned to be enrolled. Analyzed-All enrolled analysis set consisted of 517 subjects; efficacy and safety analysis set consisted of 515 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects ≥18 years of age diagnosed with MM (based on standard diagnosis criteria) and those who initiated VELCADE therapy for the approved indication, were to be enrolled.

Test Product, Dose and Mode of Administration, Batch No.: All VELCADE dosages were considered for the study. Dose adjustments and cycle delays were allowed. The recommended dosage of VELCADE was 1.3 milligram/meter^2/dose (mg/m^2/dose), administered for a 2-week treatment period with intravenous injection on Days 1, 4, 8, and 11 followed by a 10-days rest period. Each treatment cycle consisted of 21 days. The lapse between 2 doses of VELCADE was to be maintained for at least 72 hours.

Reference Therapy, Dose and Mode of Administration, Batch No.: There was no reference therapy or control used during this study.

Duration of Treatment: The duration of the study was approximately set for 3 years prospectively from the date of the subjects' initiation of VELCADE.

Criteria for Evaluation:

Primary endpoints:

VELCADE usage:

- Treatment sequence (lines of therapy)
- Dosage (unit: mg/m^2 body surface area) and duration of each dose (unit: day or length of the course)
- Subjects' diagnosis.

VELCADE therapy related results:

Efficacy:

- Disease response/progression included complete response (CR), near complete response (complete response with positive immunofixation; nCR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD); best response (best tumor response during treatment with VELCADE); Objective Response Rate (proportion of subjects with best response ≥MR; CR+nCR+PR+MR).
- Time to response (in days, from the date of first dose of VELCADE therapy until the date of the first response of CR, nCR, PR, or MR)
- Duration of response (in days, from the date on which the first response of CR, nCR, PR, or MR was documented until PD, relapse from CR [RCR], or death)
- Time to progression (in days, from the date of first dose until PD or RCR occurred), and
- Survival (in days, from the date of first dose of VELCADE until death; was to be monitored, to the extent possible, beyond the end of VELCADE therapy, up to the end of the study period).

Safety:

- Treatment-emergent AEs (TEAE)
- AEs of interest: hematology (thrombocytopenia, neutropenia, anemia and leukopenia), nervous, system (pain, paresthesia and peripheral sensory neuropathy), infection and infestations (herpes zoster and infection), and other events (bone and joint pain, cardiac events, constipation, diarrhoea, edema, emesis, liver events, pyrexia, rash and weakness).

Statistical Methods:

This was an observational study and the sample size calculation was not applicable. All enrolled analysis set was defined as the subjects who enrolled in the study, which would be used for demography and exposure analyses. Efficacy evaluable analysis set was defined as the subjects who received at least 1 study medication (with 1 or more prior treatments), which would be used for efficacy analyses. Safety analysis set was defined as all subjects who received at least 1 study medication, which would be used for safety analyses. Descriptive statistics of number of observations, mean, and standard deviation (SD), median, minimum, and maximum were summarized for continuous variables. Number and percentage of subjects were summarized for categorical variables. For time to event data, 25%, 50% (median), and 75% quartiles with associated 2-sided 95% confidence intervals (CIs) were estimated using the Kaplan-Meier (KM) method. Cox proportional hazards model was used in multiple-factor analysis for endpoints of duration of response, time to progress, and overall survival, while multiple regression model was performed for time to response. All TEAEs were summarized. Treatment-emergent adverse event was defined as any AE occurring or worsening on or after the first treatment of study drug and within 30 days after the last dose.

RESULTS:

STUDY POPULATION:

A total of 517 subjects were enrolled in the study and 515 subjects were treated. Hence, both the efficacy evaluable and the safety set consisted of 515 subjects. A summary of subject disposition is provided in the table below:

Subject Disposition (All Enrolled Analysis Set)
Study 26866138MMY4031 (VEL-CHN-MA-01)

	Total N=517 n (%)
Subjects Treated	515 (99.61%)
Subject Discontinuing Treatment (unknown)	12 (2.33%)
Subject Discontinuing Treatment	503 (97.67%)
Reason for Treatment Discontinuation*	
Financial reasons	73 (14.51%)
Remission	69 (13.72%)
Adverse Event	54 (10.74%)
Unclear	48 (9.54%)
Death	20 (3.98%)
Loss to follow-up/ Non-compliance/ Voluntary withdrawal	19 (3.78%)
Transplant	16 (3.18%)
No response/ Progression	16 (3.18%)
Use Other Chemotherapy	6 (1.19%)
Others	5 (0.99%)
Hospital beds	1 (0.20%)
Missing	176 (34.99%)

Note: *Percentages of reason for treatment discontinuation calculated with number of subjects discontinuing treatment as denominator.

The proportion of male subjects was slightly higher compared with female subjects (58.03% versus 41.97%). The mean (SD) age, weight, and height of subjects participated in this study were 58.89 (9.88) years, 63.97 (10.83) kg, and 165.77 (7.83) cm, respectively.

A total of 41.01% subjects were reported to have concomitant chronic disease. Hypertension and diabetes were the most common concomitant chronic diseases, reported in 22.24% and 10.64% of subjects, respectively. All other concomitant chronic diseases were reported in <5% of subjects. None of the subjects had human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), irritable bowel syndrome, migraine, or Parkinson's disease.

The most common lines of VELCADE treatment was third line, reported in 48.16% of subjects. Other most common lines of therapy is second line and fourth line or above, reported in 29.13% and 20.97% of subjects, respectively. The most common type of myeloma was immunoglobulin G (IgG) type MM, reported in 46.23% of subjects. Other most common type included immunoglobulin A (IgA) and light-chain type MM, reported in 23.98% and 18.96% of subjects, respectively.

The mean (SD) time from initial diagnosis to the first dose was 1.95 (3.05) years with 95% CI of 2.00, 2.00. Of note, information on time from initial diagnosis was missing for 42 subjects. Initial diagnosis for the majority (47.39%) of subjects was based on the world health organization (WHO) criteria. Other most common criteria for initial diagnosis were M-protein, south west oncology group (SWOG), European group for blood and marrow transplantation (EBMT), and Zhangzhinan used for 16.05%, 15.67%, 12.19%, and 7.35% of subjects, respectively. Based on the Durie-Salmon (DS) criteria at initial diagnosis, the majority (47.78%) of subjects were diagnosed to have stage IIIa MM. The proportion of subjects who had stage I, IIa, IIB, and IIIb MM was 4.64%, 14.70%, 3.48%, and 19.34%, respectively. The mean (SD) time to initial treatment was 1.82 (2.25) years with 95% CI of 2.00, 2.00. Of note, information on time to initial treatment was missing for 44 subjects.

The majority (44.68%) of subjects received 2 previous chemotherapies. The proportion of subjects who received 1 and ≥3 previous chemotherapy was 27.85% and 26.11%, respectively. The most common previous therapy was vincristine, adriamycin, and dexamethasone (VAD) used by 32.29% of subjects. The other most common previous therapies were immunomodulator combined therapy, vincristine, melphalan, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, and prednisone (M2/VMCP/VBAP), and melphalan and prednisone (MP), used by 16.45%, 13.66%, and 11.56% of subjects, respectively. Previous chemotherapy classified as 'others' was used by 18.01% of subjects. The majority (24.37%) of subjects had PR as the previous best response. The proportion of subjects with CR, MR, SD, and PD was 6.38%, 8.70%, 6.19%, and 6.96%, respectively. Of note, information on the previous best response is reported to be missing for 245 (47.39%) subjects.

A total of 80.27% of subjects received concomitant medications during the study. The most commonly (≥20% of subjects) used concomitant medications belonged to SMC of anti-infectives (44.68% of subjects), gastrointestinal (GI) drugs (43.33% of subjects), hematological agents (33.85% of subjects), hormones and synthetic substitutes (22.24% of subjects) and antineoplastic agents (22.05% of subjects). The most commonly (≥10% of subjects) used medications were clodronic acid (16.05% of subjects), pamidronate disodium (13.73% of subjects), mecobalamin (10.83% of subjects), and ondansetron (10.64% of subjects).

EFFICACY RESULTS:

The best response for majority (42.26%) of subjects was PR. The summary for best response is provided in the table below:

The Best Response

Study 26866138MMY4031 (VEL-CHN-MA-01)

The Best Reponses	CR	nCR	PR	MR	SD	PD	Total
Subjects	118(24.69%)	56(11.72%)	202(42.26%)	49(10.25%)	35(7.32%)	18(3.77%)	478 (100.00%)

Note: Only subjects in the evaluable efficacy analysis set who had both baseline and post baseline tumor assessment information were included in the analysis.

A clinically meaningful increase, in the proportion of subjects who achieved CR or nCR, was observed in subjects receiving VELCADE as 2/3 line of treatment from those receiving VELCADE as ≥4 line treatment. A relatively low proportion of subjects with DS stage IIB, IIIA and IIIB achieved a CR (17.65%, 24.89%, and 18.95%, respectively) compared with subjects who had DS stage I and IIA MM (29.17% and 36.11%, respectively). The proportion of subjects with CR was higher in the VELCADE 1.0 to <1.3 mg/m^2 (24.74%) and ≥1.3 mg/m^2 (29.17%) subgroups compared with the VELCADE <1.0 mg/m^2 (16.39%) subgroup. A relatively lower proportion of subjects experienced PD in the VELCADE 1.0 to <1.3 mg/m^2 (3.44%) and ≥1.3 mg/m^2 (3.33%) subgroups compared with the VELCADE <1.0 mg/m^2 (6.56%) subgroup.

Of the total 461 subjects who received VELCADE combination therapies, the majority of subjects (282 subjects) received VELCADE and dexamethasone (VD) as combination therapy. The best response in subjects who received VD was comparable to the best response in all subjects. Other combination therapies administered during the study were VELCADE, adriamycin, and dexamethasone (PAD); VELCADE, cyclophosphamide, and dexamethasone (VCD); VELCADE, melphalan, and prednisone (VMP); VELCADE and thalidomide (VT); VELCADE, thalidomide, adriamycin and dexamethasone (VTAD); VELCADE, thalidomide, and dexamethasone (VTD); and VELCADE, thalidomide, melphalan, and prednisone (VTMP). There was no notable difference observed in ORR across lines of treatment, except in “others” lines of treatment.

A substantial increase in the proportion of subjects who achieved CR was observed at the end of Cycle 8 compared with that in Cycle 1 (45.16% versus 9.91%); whereas decreases were observed in the proportion of subjects with PR (50.00% versus 38.71%), MR (15.21% versus 3.23%), and SD (12.21% versus 6.45%) from Cycle 1 to Cycle 8. The median (Q1, Q3) time to response was 27.00 (21.00, 40.00) days. Up to 120 days, >80% of subjects maintained response (CR, nCR, PR, or MR). Up to 600 days, >50% of subjects maintained response. However, the low number of subjects at risk makes the estimations after 360 days difficult to interpret.

Progression rate increased with the increased days. The progression rate (SE) was 35.85% (5.35%) for 360 days and 59.30% (9.58%) for 600 days. The survival rate (SE) was 49.93% (6.60%) for 480 days.

SAFETY RESULTS: The median of number of treatment cycles started was 3.00. A summary of TEAEs is provided below:

Summary of TEAEs (Safety Analysis Set)
Study 26866138MMY4031 (VEL-CHN-MA-01)

Terms	N subject	N events	% subject
Any TEAEs	329	1063	63.88
Drug Related TEAEs*	277	749	53.79
Serious TEAEs	33	50	6.41
Drug Related Serious TEAEs*	17	24	3.30

*Related TEAEs include probably related, possibly related and very likely related

TEAEs Leading to Death: Eighteen subjects had TEAEs leading to death, 5 of whom had drug-related TEAEs leading to death.

Overall, the most common (observed in ≥10% of the total subjects) SOCs with TEAEs were nervous system disorder (22.72% of subjects), GI disorder (22.14% of subjects), infections and infestations (21.75% of subjects). Other most common SOCs with TEAEs were general disorders and administration site conditions (19.61% of subjects), and investigations (17.67% of subjects). The incidence of most common SOCs with TEAEs under each grade was generally similar to the overall incidence. Incidence of ≥Grade 3 infection and infestations, nervous system disorders, musculoskeletal and connective tissue disorders was 4.85%, 2.52%, and 1.75%, respectively.

Overall, the most common (observed in ≥10% of the total subjects) SOCs with related TEAEs were nervous system disorders (19.61% of subjects), GI disorders (19.03% of subjects), investigations (15.73% of subjects), general disorders and administration site conditions (13.20% of subjects), infections and infestations (10.29% of subjects). Incidence of the most common SOCs with TEAEs under each grade was generally similar to the overall incidence.

Of the total 63.88% of subjects who experienced TEAEs during the study, the majority of subjects experienced Grade 1 (38.33% of subjects) and Grade 2 (33.20% of subjects) TEAEs. The proportion of subjects with Grade 3 and Grade 4 TEAEs was 16.70% and 6.41%, respectively. Overall, the most common (observed in ≥10% of the total subjects) TEAEs were platelet count decreased (14.37% of subjects), diarrhoea (13.79% of subjects), neuropathy peripheral (10.68% of subjects) and hypoaesthesia (10.10% of subjects). Other most common TEAEs were asthenia (9.9% of subjects), lung infection (7.77% of subjects), and herpes zoster (5.83% of subjects). Incidence of the most common TEAEs under each grade was generally similar to the overall incidence except Grade 4 events. The most common Grade 4 TEAE was death (2.14 % of subjects).

Of the total 53.79% of subjects who had related TEAEs (ie, possibly, probably, or very likely related) during the study, the majority of subjects had Grade 1 (32.04% of subjects) and Grade 2 (25.83% of subjects) TEAEs. The proportion of subjects with Grade 3 and Grade 4 TEAEs was 14.17% and 3.30%, respectively. Overall, the most common (observed in ≥10% of the total subjects) related TEAEs were platelet count decreased (13.79% of subjects), diarrhoea (11.65% of subjects). Other most common related TEAEs were neuropathy peripheral (9.32% of subjects), hypoaesthesia (9.32% of subjects), asthenia (8.93% of subjects), and herpes zoster (5.05% of subjects). Incidence of the most common related TEAEs under each grade was generally similar to the overall incidence.

Of the total 6.41% subjects who experienced SAEs, the majority (4.47%) of subjects experienced Grade 4 SAE. The proportion of subjects with Grade 1, Grade 2, and Grade 3 SAE was 0.19%, 0.39%, and 1.55%, respectively. Overall, the most common (observed in ≥1% of the total subjects) SOCs with SAEs were infection and infestations

(2.52% of subjects) and general disorders and administration site conditions (1.94% of subjects). The most common (observed in ≥1% of the total subjects) SAEs were death and lung infection, each reported in 1.75% of subjects.

AE of interest

AEs belonging to SOC nervous system disorders (≥85% of subjects) and SOC GI disorder (≥75% of subjects) were mild (Grade 1) to moderate (Grade 2) in intensity and considered to be related (ie, possibly, probably, or very likely related) to VELCADE by the investigator. The proportion of subjects with severe and life threatening nervous system disrorders events was 7.18% and 3.08%, respectively; 1 subject died and 9 subjects were discontinued treatment with VELCADE. The proportion of subjects with severe and life threatening GI events was 8.70% and 2.42%, respectively; 3 subjects died and 5 subjects were discontinued treatment with VELCADE.

AEs belonging to SOC infection and infestations (≥75% of subjects) were mild (Grade 1) to moderate (Grade 2) in intensity. The proportion of subjects with severe and life threatening events was 15.14% and 7.03%, respectively. In approximately 43% of subjects, infection and infestations were considered to be related (ie, possibly, probably, or very likely related) to VELCADE by the investigator. Seven subjects died and 10 subjects were discontinued treatment with VELCADE.

In the majority (≥70%) of subjects, thrombocytopenia was moderate (Grade 2) to severe (Grade 3) in intensity. The proportion of subjects with life threatening thrombocytopenia was 5.31%. In approximately 97% of subjects, thrombocytopenia was considered to be related (ie, possibly, probably, or very likely related) to VELCADE by the investigator. In the majority (≥85%) of subjects, pyrexia related events were mild (Grade 1) to moderate (Grade 2) in intensity. Approximately, 11% of subjects had pyrexia of severe intensity. None of the pyrexia related events was life threatening. In approximately 46% subjects, pyrexia was considered to be related (ie, possibly, probably, or very likely related) to VELCADE by the investigator. In the majority (≥60%) of subjects, leukopenia was mild (Grade 1) to moderate (Grade 2) in intensity. Approximately, 33% of subjects had leukopenia of severe intensity. None of the leukopenia related events was life threatening. In approximately 74% of subjects, leucopenia was considered to be related (ie, possibly, probably, or very likely related) to VELCADE by the investigator. There was no death or discontinuation of VELCADE reported due to pyrexia, thrombocytopeina and leukopenia.

The majority of hematologic AEs were recovered except anemia which was not recovered in 50% (6 subjects) of cases. Similarly, the majority of non-hematologic AEs were recovered except peripheral sensory neuropathy which was not recovered in 70.41% (69 subjects) of cases. One AE of anemia, 1 AE of liver events, 2 AEs of emesis, 3 AEs of cardiac events and 7 AEs of infection resulted in death. The frequency of AEs of interest resulting in dose adjustment and dose delay was generally low. One event of anemia, 2 events of paresthesia, 2 events of emesis, 3 events each of peripheral sensory neuropathy and cardiac events, 6 events of pain, and 9 events of infection resulted in discontinuation of medication. Overall, the majority of subjects (55.15%) had ≤Grade 2 AEs of interest. The proportion of subjects with Grade 3 and Grade 4 AEs of interest was 14.95% and 4.08, respectively. Back pain, bone pain, and fracture was reported in 6 (1.17%), 3 (0.58%), and 1 (0.19%) subjects, respectively. The majority of these events were considered to be not related to the study drug. None of these events were serious or life-threatening (Grade 4).

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

CONCLUSION(S):

This study demonstrates that VELCADE based regimen was feasible in Chinese subjects with relapse and refractory MM, provided a good response rate, and showed consistency with safety results in previous clinical trials and clinical experience.