SYNOPSIS

Name of Sponsor/Company	Johnson & Johnson Taiwan Ltd.
Name of Investigational Product	JNJ-26866138 (bortezomib)

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Protocol No.: 26866138MMY4073

Title of Study: Pharmacokinetic Study of Bortezomib (VELCADE®) Administered Intravenously in Taiwanese Patients with Multiple Myeloma - A Post Approval Commitment Study

NCT No.: NCT02268890

Clinical Registry No.: CR104583

Coordinating Investigator(s): Shang-Yi Huang, MD, PhD - National Taiwan University Hospital, Hematology, [redacted] Taiwan.

Study Center(s): The study was conducted at 7 sites in Taiwan.

Publication (Reference): None

Study Period: 05 January 2015 to 16 July 2015

Phase of Development: 4

Objectives: The primary objective of this study was to evaluate the pharmacokinetic (PK) characteristics of VELCADE when administered intravenously (IV) in Taiwanese subjects with multiple myeloma.

The secondary objective was to describe the safety and tolerability of IV administered VELCADE.

Methodology: This was a single arm, non-randomized, open-label, Phase 4 study conducted at multiple sites in Taiwan that evaluated the PK characteristics of VELCADE administered IV in Taiwanese subjects with multiple myeloma. Eligible subjects received VELCADE IV injection twice weekly for 2 weeks (on Days 1, 4, 8, and 11) and followed by a 10-day resting phase (Days 12 to 21) for 1 treatment cycle, then followed by an End of Study visit which was done within 30 days (but no earlier than last PK sample collection) of last dose of VELCADE in the study. Blood samples were collected on Days 1, 11, 12, 13, and 14 for PK analysis. Subjects were considered to have completed the study once the study treatment, PK sample collection and the End of Study visit were completed. After End of Study visit, the subjects were released from the study and routine medical care was provided by subjects' attending physician according to routine clinical practice. For subjects' benefit and ethical consideration, the sponsor provided VELCADE for up to 7 continuous cycles according to the approved indication and investigator's medical judgment.

Number of Subjects (planned and analyzed): Planned enrollment was approximately 18 subjects to achieve 12 PK-evaluable subjects. Eighteen subjects were enrolled in the study and all subjects were considered evaluable for PK. All enrolled subjects received study agent and were included in the safety population.

Diagnosis and Main Criteria for Inclusion: Subjects eligible for this study were male or female ≥20 years of age with a diagnosis of multiple myeloma, who had Karnofsky performance status (KPS) ≥70% and underwent relapse or progression of myeloma. Subjects must have had measurable secretory multiple myeloma, defined as serum monoclonal IgG of ≥10 g/L, serum monoclonal IgA or IgE ≥5 g/L, serum monoclonal IgD ≥0.5 g/L, or serum monoclonal IgM present (regardless of level), or urine M protein of ≥200 mg/24 hour at any time point of prior treatment. Subjects must not have received more than 3 previous lines of therapy; antineoplastic or experimental therapy, corticosteroid above 10 mg/day (prednisone or equivalent), or plasmapheresis within 3 weeks prior to enrollment in the study; or not have had peripheral neuropathy or neuropathic pain of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 Grade ≥2. Subjects must not have undergone radiation therapy and major surgery (kyphoplasty excluded) within 2 weeks prior to enrollment in the study.

Test Product, Dose and Mode of Administration, Batch No.: VELCADE for injection is an antineoplastic agent for IV use. Subjects received 1.3 mg/m^2/dose of VELCADE, IV, on Days 1, 4, 8, and 11. The dose (in mg) of drug to be administered was based on body surface area (BSA). Subjects received VELCADE at a concentration of 1 mg/mL (3.5 mg bortezomib reconstituted with 3.5 mL normal [0.9%] saline) as a 3- to 5-second IV push for PK evaluation. The lot numbers of VELCADE used in this study were: DKZSV00 (expiration date: 31 October 2016) and EEZV300 (expiration date: 30 April 2017).

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable

Duration of Treatment: Eligible subjects received VELCADE IV injection twice weekly for 2 weeks (on Days 1, 4, 8, and 11) in the study.

Criteria for Evaluation:

Pharmacokinetics: For the evaluation of the steady state PK profile of VELCADE, blood samples to determine the concentrations of VELCADE in plasma were collected on Day 1 predose and at the following times starting on Day 11: at 0 hours (within approximately 30 minutes before dosing), and at 2-, 5-, 15-, and 30-minutes, and at 1-, 2-, 4-, 6-, 10-, 24- (Day 12), 32- (Day 12), 48- (Day 13), and 72-hours (Day 14) after the Day 11 VELCADE administration.

Concentrations of VELCADE in plasma were determined using a validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method. PK parameters were estimated by non-compartmental analysis of the plasma concentration-time data.

A venous blood sample of 5 mL was collected at each time point. Specimens (approximately 75 mL per subject in total) for PK evaluation were kept frozen at –70°C or lower until analyzed for determination of plasma drug concentration. All calculations were based upon the reported concentrations and sampling times.

All concentrations below the limit of quantification (LOQ) or missing data were labeled as such in the concentration data listings. Concentrations below the LOQ were treated as zero in the summary statistics and for the calculation of PK parameters.

Factors that might influence the plasma concentrations (eg, co-medication, fever, high predose concentration) were evaluated. All data were included in the PK analysis. One subject took fluconazole (a moderate CYP3A inhibitor) on Days 1-8, which was not considered to have an impact on the PK assessment on Day 11.

Safety: Safety and tolerability assessments were based on the observation or report of any adverse events (AEs) (including laboratory abnormalities reported as AEs) from the signing of informed consent to 30 days after the last dose of study agent. The intensity (severity) of AEs was assessed using NCI CTCAE, Version 4.03. In addition, changes in physical examinations, KPS, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) scores, heart rate,

blood pressure, temperature, and clinical laboratory findings from baseline through the End of Study visit were also assessed.

Statistical Methods:

Sample size determination: The intersubject coefficient of variation (CV) for area under the curves (AUCs) and maximum observed plasma concentration (C_{max}) following administration of VELCADE IV in subjects with multiple myeloma was estimated to be 29% and 45%, respectively, based on a previous study. A sample size of 12 subjects was sufficient to estimate the geometric mean AUCs and C_{max} of VELCADE to be within 80% ~ 125% and 75% ~ 133% of their true values, respectively, with 95% confidence. In order to obtain 12 evaluable subjects to complete PK evaluation, the enrollment of approximately 18 Taiwanese subjects with multiple myeloma was planned.

Pharmacokinetics: The PK-evaluable population included all subjects who completed all PK sample collection during the study without a dose omission, delay, or modification. All PK parameter values were summarized with descriptive statistics. For each subject, plasma concentration versus time profile was plotted. Mean plasma concentration-time profiles were also plotted. Plasma concentration data at each time point were summarized with mean, standard deviation (SD), and CV. All estimated PK parameter values were summarized with mean, median, geometric mean, minimum, maximum, SD, and CV. PK parameters were compared to PK results obtained in a separate study (26866138-CAN-1004: hereafter referred to as CAN1004) in subjects with multiple myeloma conducted overseas, using the same dosing regimen and PK sampling schedule.

Safety: The safety analysis set (ie, the safety population) was defined as all subjects who received at least 1 dose of study agent. Safety analyses were based on safety analysis set. Safety was summarized using the incidence, relationship to study agent and intensity of AEs, vital signs (temperature, heart rate and blood pressure) measurements and physical examinations, KPS scores, FACT/GOG-Ntx scores, electrocardiogram, clinical hematology and chemistry laboratory tests. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18. The frequency and percentage of subjects with at least one treatment-emergent AE were summarized according to intensity (NCI CTCAE, Version 4.03) and drug relationship as well as categorized by system organ class (SOC) and preferred term.

RESULTS:

STUDY POPULATION:

Overall, 18 subjects received at least 1 dose of study agent and therefore by definition represents the safety population for this study. All subjects (18) in the safety analysis set completed the study.

All subjects (18 subjects; 100%) were Asian. Of the 18 subjects in the safety analysis set, 11 (61.1%) were male and 7 (38.9%) were female. The median age was 62.5 years (range 49 to 84 years), with 44.4% of subjects ≥65 years of age; the median BSA was 1.635 m^2 (range 1.38 to 2.05 m^2); and the median body mass index (BMI) was 24.455 kg/m^2 (range 18.75 to 29.99 kg/m^2). Of the 18 subjects, 10 subjects (55.6%) had a baseline KPS score of 90, which denotes that the subject was able to carry on normal activity, but had minor signs or symptoms of disease and 8 subjects (44.4%) had a baseline KPS score of 80, which denotes that the subject could carry on normal activity with effort, but had some signs or symptoms of disease.

A total of 6 subjects had at least 1 major protocol deviation. Major protocol deviations included “Other” reasons (4 subjects), subjects who received a disallowed concomitant treatment (2 subjects), and a subject who entered the study but did not satisfy the entry criteria (1 subject). “Other” reasons included missing data and PK collected outside the protocol-specified window period. The deviations identified did not have an impact on the overall conclusions of the study. Based on the PK and clinical review of the data, these major protocol deviations had no effect on the PK or safety findings of the study.

All subjects (18) received VELCADE IV on Days 1, 4, 8, and 11. The median dose of VELCADE administered to subjects on Days 1, 4, 8, and 11 was 2.10 mg.

PHARMACOKINETIC RESULTS:

Bortezomib PK parameters from the current study are summarized in the table below along with historical data from Study CAN1004. Overall bortezomib exposure (AUC) was comparable between Taiwanese subjects and non-Asian subjects who had blood samples collected using the same procedures. The maximum concentration (observed C_{max}) and the initial concentration by extrapolation to time zero (C_0) were higher in Taiwanese subjects.

Mean (SD) Bortezomib Pharmacokinetic Parameters in Taiwanese and Non-Asian Subjects With Multiple Myeloma (Study 26866138MMY4073: Pharmacokinetics Data Analysis Set)

	MMY4073 (n=18)			CAN1004 (n=10)		
Parameter	Mean (SD)	CV	+/-Precision	Mean (SD)	CV	+/-Precision
Day 11 predose (ng/mL)	2.03 (3.01)			2.45 (2.33)		
C_0 (ng/mL)	442 (167)			321 (181)		
t_{max} (h)[a]	0.03 (0.03 - 0.04)			0.03 (0.03 - 0.05)		
C_{max} (ng/mL)	266 (77.5)	29%	(87%, 116%)	162 (79.9)	50%	(70%, 143%)
- Geometric mean	257			131		
AUC_{last} (ng.h/mL)[b]	230 (147)	64%	(73%, 137%)	241 (82.0)	34%	(78%, 128%)
- Geometric mean	203			229		

[a] Median (range)
[b] 72 hours

SAFETY RESULTS:

VELCADE administered IV in Taiwanese subjects with multiple myeloma was generally well tolerated. No new safety signals were observed.

Adverse Events: All subjects (18 [100%]) in the VELCADE group experienced at least 1 treatment-emergent adverse event (TEAE) during the study. Drug-related AEs (ie, considered by the investigator, to be possible, probable, or very likely related to the study agent) were reported in 14 subjects (77.8%). A higher percentage of subjects were noted to have Grade 1 and Grade 2 TEAEs (14 subjects [77.8%] each) than Grade ≥3 TEAEs (10 subjects [55.6%]). The 3 SOCs with the highest incidence of TEAEs were Blood and lymphatic system disorders (15 subjects [83.3%]), Gastrointestinal disorders (10 subjects [55.6%]), and Infections and infestations (8 subjects [44.4%]). The SOC with the highest proportion of subjects with Grade 3 (6 subjects [33.3%])/Grade 4 (3 subjects [16.7%]) TEAEs and with 1 or more drug-related AEs (11 subjects [61.1%]) was within the Blood and lymphatic system disorders SOC. The most commonly (occurred in ≥ 3 subjects) reported Grade 3 TEAEs were neutropenia (7 subjects [38.9%]), thrombocytopenia (4 subjects [22.2%]), and leukopenia (3 subjects [16.7%]) and Grade 4 TEAE was thrombocytopenia (3 subjects [16.7%]).

Death: One (5.6%) subject died after study completion, but within 30 days following the last dose of study agent, and the causes of death were pneumonia (not related) and cardiac failure (doubtfully related).

Serious Adverse Events (SAEs): Five subjects (27.8%) reported 1 or more serious TEAEs. Among them, 1 subject experienced a drug-related serious TEAE of pneumonia. The highest proportion of subjects with treatment-emergent SAEs was within the Infections and infestations SOC (3 subjects [16.7%]). The most common (occurred in ≥2 subjects) treatment-emergent SAE was pneumonia (2 subjects [11.1%]).

AEs Leading to Dose Adjustment or Discontinuation of Study Agent: One of the 18 subjects had a dose reduction due to a TEAE of thrombocytopenia. None of the TEAEs led to permanent discontinuation of the study agent.

Karnofsky Performance Status: KPS demonstrate an overall similarity in the performance scores during the screening period, on Day 1, and at the End of Study visit.

FACT/GOG-Ntx Scores: There was no appreciable difference in the mean (SD) FACT/GOG scores at baseline (45.11 [8.663]) and at the End of Study visit (45.11 [9.536]). The mean (SD) Ntx score was 11.44 (7.905) at baseline and 9.67 (6.059) at the End of Study visit.

Laboratory Assessments: Laboratory assessments did not identify any new safety signals.

Vital Signs and Physical Findings: No clinically notable changes were recorded in the mean systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, temperature, or weight during the study.

STUDY LIMITATIONS:

Since the subjects received only 1 cycle of IV VELCADE treatment to evaluate PK characteristics, the efficacy of treatment was not evaluated.

CONCLUSIONS:

Overall bortezomib exposure (AUC) in Taiwanese subjects after IV VELCADE injection twice weekly (on Days 1, 4, 8, and 11) for the first 2 weeks of one 3-week treatment cycle was 230 ng.h/mL, which is comparable with historical data in non-Asian subjects.

IV VELCADE injection was well tolerated by Taiwanese subjects with multiple myeloma with no unexpected safety concerns.

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