1 Title

Study Title	A Phase I/II Study of JNJ-26866138 (bortezomib) in Japanese Patients with Relapsed or Refractory Multiple Myeloma
Study Drug Name	JNJ-26866138
Indication	Relapsed or refractory multiple myeloma
Study design, control drug, duration of treatment, dosage, patient population	・A non-randomized open-label study (multicenter open-label study), without a control. ・JNJ-26866138 intravenously administered as a single-agent once daily, twice a week, for 2 weeks (Days 1, 4, 8 and 11), followed by a 10-day rest period (Days 12 to 21). This was considered one cycle (21 days), and treatment was given up to 6 cycles at maximum. ・In the phase I part, the initial dose was 0.7 mg/m^2, which was escalated to 1.0 mg/m^2 and 1.3 mg/m^2 in two steps. ・In the phase II part, treatment was conducted at the Japanese recommended dose (RD) determined in the phase I part. ・Patients aged at least 20 and younger than 75 who had an established diagnosis of multiple myeloma.
Sponsor name	Janssen Pharmaceutical K.K.
Protocol number	JNJ-26866138-JPN-MM-101 CR009058
Developmental phase	Phase I/II
Starting date of study	May 7, 2004 (first patient enrolled)
Early study discontinuation	None
Final date of study	January 16, 2006 (last patient completed)
Medical Advisor	Ryuzo Ueda, Professor, Internal Medicine and Molecular Science, Nagoya City University Graduate School of Medical Sciences
Study Director/ Contact of person in charge	Study Director: Ryo Ishida (Clinical R&D Department 1, Clinical Research & Development Division) Person in charge: Yoshitaka Kotobuki (Clinical R&D Department 1, Clinical Research & Development Division) 5-2, Nishi-kanda 3-chome, Chiyoda-ku, Tokyo 101-0065 TEL: 03-4411-5059 FAX: 03-4411-5089
GCP Statment	This clinical study was conducted in deference to ethical principles based on the Declaration of Helsinki, and in conformity to the standards provided in the Pharmaceutical Affairs Law, Article 14, Paragraph 3 and Article 80-2, MHW Ordinance No. 28 “Ordinance related to the Good Clinical Practice” (March 27, 1997), MHW Ordinance No. 36 (March 26, 2001), MHW Ordinance No. 106 (June 12, 2003), PAB Notification No. 430 (March 27, 1997) “Enforcement of the Ordinance related to the Good Clinical Practice”, PFSB/ELD Notification No. 0722014 (July 22, 2004) “Operation of the Good Clinical Practice”, and CPAC Notification No. 40 (March 13, 1997) “Contents of the Good Clinical Practice (GCP)” (CPAC-GCP). All the study-related documents and materials have been stored adequately at the respective responsible departments.
Date of report	December 19, 2006

2 Synopsis

<table>
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Janssen Pharmaceutical K.K.</td><td rowspan="3">Summary table of clinical study
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<tr><td>Product name: Velcade</td></tr>
<tr><td>Active ingredient:
bortezomib</td></tr>
<tr><td colspan="3">Study title:
A Phase I/II Study of JNJ-26866138 (bortezomib) in Japanese Patients with Relapsed or Refractory Multiple Myeloma</td></tr>
<tr><td colspan="3">Investigators:
Tomomitsu Hotta, Kensei Tobinai, Hironobu Minami, Yasuo Morishima</td></tr>
<tr><td colspan="3">Study Center(s):
Tokai University Hospital, National Cancer Center Hospital, National Cancer Center Hospital East, Aichi Cancer Center</td></tr>
<tr><td colspan="3">Published papers (cited references):
Kensei Tobinai, Takashi Watanabe, Yoshiaki Ogawa, Michinori Ogura, Yasuo Morishima, Hironobu Minami, et al. Pharmacokinetic (PK) and Pharmacodynamic (PD) Profiles of Bortezomib (B) in Patients (pts) with Relapsed Multiple Myeloma (MM): A Phase I/II Study in Japan. Blood. 2006 Nov 16;108(11):365b-6b.
(For cited references: see Chapter 15)</td></tr>
<tr><td colspan="2">Study Period:
First patient enrolled: May 7, 2004
Last patient completed: January 16, 2006</td><td>Phase of Clinical Study:
Phase I/II</td></tr>
<tr><td colspan="3">Objectives:
<u>Phase I part</u>
Primary objectives:
To assess the safety/tolerability and determine the Japanese RD of JNJ-26866138 administered as a once-daily intravenous bolus twice weekly for 2 consecutive weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12 to 21) in Japanese patients with relapsed or refractory multiple myeloma (MM). The daily dose of JNJ-26866138 will be increased up to 1.3 mg/m^2 (dose level 3; overseas RD) and the tolerability will be examined in this Japanese population in order to determine the Japanese RD.
Secondary objectives:
1) To determine the plasma concentration of unchanged bortezomib to examine the pharmacokinetics (PK).
2) To examine the efficacy (antitumor activity) of JNJ-26866138.
3) To determine 20S proteasome inhibition in whole blood to examine the pharmacodynamics (PD) of JNJ-26866138.
<u>Phase II part</u>
Primary objectives:
Continue patient accrual at the Japanese RD determined in the phase I part to examine the efficacy (antitumor activity) and safety after treatment with JNJ-26866138 given as a single-agent in Japanese patients with relapsed or refractory MM.</td></tr>
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Product name: Velcade		
Active ingredient: bortezomib		

Secondary objectives:

To examine the time to progression (TTP), survival, and time to response and duration of response.

Study Methods:

The study was a multicenter, non-randomized, open-label study in patients with relapsed or refractory multiple myeloma, where JNJ-26866138 was intravenously administered as a single-agent once daily, twice weekly for 2 weeks (Days 1, 4, 8, and 11), followed by a 10-day rest period (Days 12 to 21). This was considered one cycle (21 days), and treatment was repeated up to 6 cycles in patients expected to show a response to the therapy. Treatment with the study drug was discontinued in patients judged to have a progressive disease (PD) by the evaluation of efficacy (investigator assessment) in both phase I and phase II parts.

Phase I part

Using the initial dose of 0.7 mg/m^2 (dose level 1), a two-step dose escalation to 1.0 mg/m^2 (dose level 2) and 1.3 mg/m^2 (dose level 3: overseas RD) was planned. The Japanese RD was determined from the tolerability in Japanese patients when the dose was increased from 0.7 mg/m^2 to 1.3 mg/m^2 at maximum. If there were no tolerability issues and dose increases up to 1.3 mg/m^2 was possible, the study was to advance to the phase II part using the overseas RD 1.3 mg/m^2 as the Japanese RD. In addition, pharmacokinetic assessments and pharmacodynamics assessments were planned for patients in the phase I part.

Phase II part

Enrollment of additional patients was to be conducted up to 24 patients including the patients treated at the Japanese RD in the phase I part in order to assess the antitumor effect and safety.

Number of Subjects (planned and analyzed):

Phase I part

Planned: Minimum 15 patients (pts)*

*When dose limiting toxicity (DLT) occurs in at least 1/3 or 2/6, additional subjects will be enrolled as needed based on calculation according to the continuous reassessment method (CRM).

Analyzed: Number of enrolled patients: 16 pts (0.7 mg/m^2: 3 pts, 1.0 mg/m^2: 6 pts, 1.3 mg/m^2: 7 pts)

Primary efficacy analysis set: 15 pts (0.7 mg/m^2: 3 pts, 1.0 mg/m^2: 6 pts, 1.3 mg/m^2: 6 pts)

Safety analysis set: 16 pts (0.7 mg/m^2: 3 pts, 1.0 mg/m^2: 6 pts, 1.3 mg/m^2: 7 pts)

DLT analysis set: 15 pts (0.7 mg/m^2: 3 pts, 1.0 mg/m^2: 6 pts, 1.3 mg/m^2: 6 pts)

Pharmacokinetic /pharmacodynamics analysis set: 16 pts (0.7 mg/m^2: 3 pts, 1.0 mg/m^2: 6 pts, 1.3 mg/m^2: 7 pts)

Phase II part

Planned: 24 pts (including patients treated at the Japanese RD in the phase I part)

Analyzed: Number of enrolled patients: 25 pts (including 7 patients treated at 1.3 mg/m^2 in

the phase I part)

Primary efficacy analysis set: 24 pts (including 6 patients treated at 1.3 mg/m^2 in the phase I part)

Safety analysis set: 25 pts (including 7 patients treated at 1.3 mg/m^2 3 in the phase I part)

Diagnosis and Major Inclusion Criteria

Patients who met all of the following criteria were eligible as patients for the study.

1) Patients diagnosed with multiple myeloma based on the predetermined diagnostic criteria.

2) Patients who received at least standard first-line therapy and had documentation of failure to that therapy or relapsed after remission and currently requires therapy because of progressive disease (PD) as assessed by the investigator (subinvestigator) at enrollment. There is no limitation in the number of prior therapies (salvage therapies; number of regimens).

3) Patients with measurable disease, defined as follows.

Secretory Multiple myeloma	・Quantifiable serum monoclonal protein value (in general, serum M protein values of ≥ 1.0 g/dL of IgG and ≥ 0.5 g/dL of IgA.) ・When M protein is excreted in urine, M protein is quantitatively assayable by urinary protein electrophoresis (in general, urinary M protein excretion of ≥ 0.2 g/day.)
Nonsecretory Multiple myeloma	・Presence of bidimensionally measurable soft tissue masses (plasmacytomas) with a longer diameter of 2 cm and more as determined by applicable radiographies (i.e. MRI, CT-scan).

4) Patients with a life expectancy of ≥ 3 months after initiation of JNJ-26866138 therapy.

5) Patients with a Karnofsky Performance Status (PS, general condition) of ≥ 60.

6) Patients aged at least 20 and younger than 75 at enrollment in the study.

7) Patients who can be hospitalized at least from the initial treatment of the study drug to the completion of Cycle 1 (including the 10-day observation period after JNJ-26866138 injection)*.

* When the next cycle is delayed because the "conditions for the start of the next cycle" were not satisfied, patients must be hospitalized until the patient satisfies the criteria (it is possible to transfer patients to treatment on an outpatient basis when the next cycle is delayed due to reasons such as schedule adjustment).

8) Patients with adequate major organ function who fulfill all of the following criteria within 14 days of Day 1 (N=Upper limit of institutional reference range):

1. Bone marrow function

Neutrophil count ≥1,000/mm^3 (Values without using G-CSF within 7 days prior to the test)
Platelet count ≥75,000/mm^3 (Values without platelet transfusion within 7 days prior to the test)
Hemoglobin ≥8.0 g/dL (Values without red blood cells transfusion within 7 days prior to the test)

2. Liver function
   Serum total bilirubin ≤1.5×N
   ALT（SGPT）≤2.5×N
   AST（SGOT）≤2.5×N
3. Renal function
   Creatinine clearance ≥30 mL/min
4. Electrolytes
   Corrected serum calcium ≤12.5 mg/dL (3.1 mmol/L)
   Serum sodium >130 mEq/L
5. Cardiac function
   No abnormal findings requiring treatment on both electrocardiograms and echocardiograms.

9) Patients with no evident effect of prior treatment who fulfill the following criteria until the day of enrollment:

・Chemotherapy, steroid therapy (except for topical agents), thalidomide, and interferon
  Patients must have their last dose at least 4 weeks before treatment initiation (6 weeks for nitrosoureas).
・Immunotherapy (except for interferon)
  Patients must have their last treatment at least 8 weeks before treatment initiation of the study drug.
・Autologous stem cell transplantation
  Patient must have the transplant at least 8 weeks before treatment initiation of the study drug.
・Antibody therapy
  Patients must have their last treatment at least 12 weeks before treatment initiation of the study drug.
・Radiation therapy
  Patients must have their last treatment at least 4 weeks before treatment initiation of the study drug.
・Blood plasma exchange (plasmapheresis) and extensive surgery*
  Patients must have their last treatment at least 4 weeks before treatment initiation of the study drug.
  * Extensive surgery does not include kyphoplasty (cement fixation of compression fracture).
・Use of other investigational products

Patients who had been treated with any investigational product that is not currently marketed in Japan, irrespectively of the purpose of use, must have had their last dose at least 12 weeks before treatment initiation of the study drug.

10) Female patients who are either post-menopausal (≥1 year after the last menstruation) or surgically sterilized, or willing to use an acceptable method of birth control (e.g., a hormonal contraceptive, contraception device) for the duration of the study. Male patients who agree to use an acceptable method for contraception for the duration of the study.
11) Patients who are informed of the details of the study with the specified informed consent form and other written information for subjects by the investigator or subinvestigator (and clinical trial collaborator) and has given voluntary written informed consent for study participation.

Test product, dose and mode of administration, lot number:

Dosage

Based on the body surface area calculated before treatment in each cycle, the dosage was calculated for each patient according to the dose level specified by the Patient Enrollment Center (0.7mg/m^2, 1.0 mg/m^2 or 1.3 mg/m^2).

Mode of administration

JNJ-26866138 was intravenously administered once daily, twice weekly for 2 weeks (Days 1, 4, 8, and 11), followed by a 10-day rest period (Days 12 to 21). This was considered one cycle (21 days), and treatment was repeated up to 6 cycles in patients expected to show a response to the therapy. JNJ-26866138 solution was intravenously administered over 3 to 5 seconds, and flushed with physiological saline.

Lot number of study drug

Lot numbers of JNJ-26866138: 01BK, 02DA, 03DG

Duration of treatment:

One cycle (21 days), up to 6 cycles

Criteria for evaluation:

Phase I and Phase II parts

Safety:

Subjective symptoms, objective findings, physical examination (vital signs, body weight), laboratory examinations (hematological examination, blood chemistry test, urinalysis, ECG, echocardiogram, chest X-ray, chest CT), neurological examination, performance status (PS)

Efficacy:

Antitumor activity (determination of serum/urinary M protein concentration, bone marrow aspiration or biopsy, tumor reduction effect, observation of osteolytic lesions, corrected serum calcium value), TTP, overall survival, and time to response and duration of response

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Phase I part only

DLT:

≥Grade 3 non-hematological adverse events suspected to be related with the study drug* and Grade 4 hematological adverse events (adverse drug reaction) are defined as DLT. The evaluation of toxicity findings was conducted according to the JCOG Japanese translation (Version 2) of NCI-CTC Ver. 2.

*All events except events whose relationship with the study drug was judged as "Not related" or "Doubtful".

Pharmacokinetics: Plasma concentration of unchanged bortezomib

Pharmacodynamics: Percent inhibition of 20S proteasome activity in whole blood

Statistical Methods:

Safety

The following statistical analyses were conducted in the safety analysis set in all dose levels and per each dose level.

1) The number of patients with adverse events and the incidence were tabulated by severity and causality with the study drug. The incidence of DLT in the first treatment cycle and all treatment cycles that was confirmed in the DLT analysis set were analyzed in the same manner.
2) Tables were prepared that contain the following: contents of adverse events (including abnormal changes in laboratory test values), dose level, treatment cycle, severity, seriousness, onset date, outcome, and causality, etc.
3) Descriptive statistics were calculated for test values of the hematological examination and blood chemistry test by testing time, and Wilcoxon signed rank test was conducted for the difference from baseline.
4) For patients who had ≥Grade 1 hematological toxicities (white blood cell decreased, neutrophil count decreased, platelet count decreased, hemoglobin decreased) whose relationship with the study drug could not be ruled out, the time to confirm the nadir of the value of hematological examination and the required time to recovery/relief were calculated.

Efficacy

The response rate was calculated in the full analysis set (FAS) and per protocol set (PPS) per dose level. Primary analysis was performed in the FAS. For sensitivity analysis, analyses in the PPS were also performed.

Pharmacokinetics (Phase I part)

Pharmacokinetic parameters were calculated in the Pharmacokinetic /pharmacodynamics analysis set using individual determination values of the plasma concentration of unchanged bortezomib on Day 1 and Day 11 in Cycle 1. By comparison of pharmacokinetic parameters on Day 1 and Day 11, the presence or absence of accumulation was examined, and exploratory analyses such as comparison of pharmacokinetic

parameters with those obtained in an overseas clinical study (Study M34103-058), assessment of dose-relationship, and consideration of patient characteristics were added as needed.

Pharmacodynamics (Phase I part)

Based on individual blood 20S proteasome activity values on Day 1 and Day 11 in Cycle 1, the inhibition rate of blood 20S proteasome activity in the Pharmacokinetic /pharmacodynamics analysis set at each determination point was calculated from a comparison with baseline activity value to assess the relationship with the plasma concentration of unchanged bortezomib. Exploratory analyses such as comparison of the inhibition rates of blood 20S proteasome activity with those obtained in an overseas clinical study (Study M34103-058), assessment of dose-relationship, and consideration of patient characteristics were added as needed.

Summary and Conclusions:

Determination of RD in Japan

The tabulation was conducted using a data cut-off date of February 2, 2005, when the DLT assessment of the final patient treated at dose level 3 (1.3 mg/m^2) in Cycle 1 in the phase I part was finished. As a result, among the 15 patients in the DLT analysis set, DLTs occurred in 5 patients. DLTs observed up to the end of observation in Cycle 1 was only 1 event in 1 patient in the 1.3 mg/m^2 dose group (16.7%, 1/6). In Cycle 2 and after, 3 events of DLT were observed in 3 patients in the 1.0 mg/m^2 dose group (50.0%, 3/6), and 1 event was observed in 1 patient in the 1.3 mg/m^2 dose group (16.7%, 1/6). In addition, by comprehensive consideration of the occurrences of toxicity and recovery in Cycle 2 and after, the frequency of treatment delay or treatment discontinuation and their content, and results of pharmacokinetics, based on the recommendation of the Independent Data Monitoring Committee (IDMC) and the Medical Advisor, 1.3 mg/m^2 was selected as the Japanese RD when the study drug was intravenously administered once daily, twice weekly, for 2 weeks (Days 1, 4, 8 and 11), followed by a 10-day rest period (Days 12 to 21).

Finally, among the 15 patients in the DLT analysis set, DLT was observed in 6 patients when data after the cut-off is included. After the data cut-off, 3 events of DLT were observed in 2 patients in the 1.3 mg/m^2 dose group in Cycle 2 or after.

Summary of pharmacokinetic and pharmacodynamics assessments

The plasma concentration of unchanged bortezomib showed a biphasic decrease characterized by a rapid distribution phase and the subsequent slow and long elimination phase at all doses. A delay in elimination of unchanged bortezomib in plasma associated with repeated-dose administration was observed, and accordingly, C_0 and AUC both showed higher values on Day 11 compared with Day 1. As a result of the dose relationship assessment, no dose relationship was observed for C_0, but dose relationship

was observed for $AUC_{(0\rightarrow t)}$ and AUC on each study day. As a result of the pharmacodynamics assessment, it was revealed that unchanged bortezomib showed a reversible, persistent and potent inhibition of 20S proteasome activity in blood with dose increase and repeated administration. When results of this study and pharmacokinetic and pharmacodynamic results of the overseas study (Study M34103-058) were compared, no clear differences suggesting an ethnic difference was observed.

Efficacy Summary

In the evaluation of antitumor activity, for patients of the efficacy analysis set whose evaluation of the physician in charge was MR or better, a central evaluation was conducted by the Independent Review Committee (IRC). The efficacy analysis was conducted based on their results. The last observation date of efficacy was April 6, 2006.

The response rate in patients treated at the Japanese RD (1.3 mg/m^2) was 33.3%, and the 90% CI was [17.8, 52.1]. For the response rate in patients treated at the Japanese RD, the lower limit of CI was confirmed to exceed the threshold response rate 5%. The response rate (CR+PR) in the whole FAS was 30.3% (10/33). Among the dose groups, no patient showed a response in the 0.7 mg/m^2 dose group, and the response rate in the 1.0 mg/m^2 and 1.3 mg/m^2 dose groups were both 33.3% (2/6 and 8/24, respectively). The median TTP [95% CI] of patients treated at the Japanese RD (1.3 mg/m^2) was 160.0 days [144.0, 208.0]. The number of patients whose PD was confirmed at the last observation date was 8, and the number of censored patients was 16. The number of deaths in patients treated at the Japanese RD (1.3 mg/m^2) up to the last observation date was 3 patients, and no estimated value of overall survival could be obtained. The mean time to response [95% CI] in the 8 patients who attained response after treatment at the Japanese RD (1.3 mg/m^2) was 47.5 days [39.0, 96.0]. Among the 8 patients who responded, only 1 patient showed PD after response had been confirmed by the last observation date, and the duration of response was 122 days.

Safety Summary

Adverse events occurred in all of the 34 patients of the safety analysis set. At least 1 adverse event was judged as related to the study drug (adverse reaction: adverse events whose causality with the study drug was judged as “Doubtful”, “Possible”, “Probable” or “Very likely”) in all patients. Adverse events that were observed at a high frequency (incidence ≥50%) include anemia (73.5%, 25/34), lymphocyte count decreased (64.7%, 22/34), diarrhea and constipation (55.9%, 19/34, respectively), anorexia, nausea, pyrexia, neutrophil count decreased and white blood cell count decreased (52.9%, 18/34, respectively). Hematological adverse events and gastrointestinal disorders were predominant. Adverse events that occurred at a high frequency (incidence ≥50%) by SOC were Investigations (97.1%, 33/34), gastrointestinal disorders (94.1%, 32/34), metabolism

and nutrition disorders (91.2%, 31/34), general disorders and administration site conditions (85.3%, 29/34), blood and lymphatic system disorders (82.4%, 28/34), nervous system disorders (70.6%, 24/34), skin and subcutaneous tissue disorders (61.8%, 21/34), infections and infestations (55.9%, 19/34), and musculoskeletal and connective tissue disorders (55.9%, 19/34). ≥Grade 3 adverse events occurred in 88.2% (30/34). Among ≥Grade 3 adverse events, hematological adverse events were prevalent. Neutrophil count decreased occurred in 38.2% (13/34). Anemia and lymphocyte count decreased occurred in 32.4% (11/34) respectively, and neutropenia occurred in 26.5% (9/34). Lymphopenia and white blood cell count decreased occurred in 23.5% (8/34) respectively. Of non-hematological adverse events, the ≥Grade 3 adverse event that occurred at the highest incidence was pneumonia (8.8%, 3/34). ≥Grade 4 adverse events occurred in 26.5% (9/34). Neutropenia and neutrophil count decreased occurred in 8.8% (3/34) respectively, and hematuria, blood amylase increased, and blood uric acid increased occurred in 2.9% (1/34) respectively. Serious adverse events were reported in 20.6% (7/34). The reported serious events include interstitial lung disease in 2 patients (5.9%, 2/34), and pleural effusion, hematuria, pneumothorax, sepsis, thrombocytopenia, febrile neutropenia, enterococcal sepsis, pneumonia, bronchopneumonia, and enteritis in 1 patient (2.9%, 1/34) respectively. There was a death in 1 patient due to interstitial lung disease that occurred during the study period. This patient died 88 days after the final treatment with the study drug due to interstitial lung disease that occurred 2 days after the third dose in Cycle 2. The causal relationship of the interstitial lung disease with the study drug was judged as "Very likely".

Conclusion

JNJ-26866138 was intravenously administered in patients with relapsed or refractory multiple myeloma twice weekly for 2 weeks (Days 1, 4, 8, and 11), followed by a 10-day rest period (Days 12 to 21). The safety was assessed considering this one cycle, and as a result, the RD in Japan was determined as 1.3 mg/m^2. Administration of JNJ-26866138 at the Japanese RD (1.3 mg/m^2) was demonstrated to have an antitumor effect for patients with multiple myeloma refractory to standard therapy or relapsed after remission induction. With regard to its safety, although attention must be paid to serious lung disorders, other adverse reactions were considered clinically manageable.

Date of Report: December 19, 2006

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