CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021602Orig1s027

Trade Name: **Velcade**

Generic Name: **bortezomib**

Sponsor: **Millennium Pharmaceuticals, Inc.**

Approval Date: 01/23/2012

Indications: VELCADE is a proteasome inhibitor indicated for:
• treatment of patients with multiple myeloma
• treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021602/S-027

SUPPLEMENT APPROVAL

Millennium Pharmaceuticals, Inc.
Attention: Eileen Bedell, M.P.H
Director, Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Bedell:

Please refer to your Supplemental New Drug Application (sNDA) dated March 23, 2011, received March 23, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VELCADE® (bortezomib) for Injection.

We acknowledge receipt of your amendments dated April 7 and 29, June 30, July 22, September 14 and 20, October 4 and 13, November 15 and 16, and December 22, 2011.

This "Prior Approval" supplemental new drug application provides for a subcutaneous route of administration as an alternative to the existing intravenous route of administration.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 021602/S-027**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Acting Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDVARDAS KAMINSKAS
01/23/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VELCADE safely and effectively. See full prescribing information for VELCADE.

VELCADE® (bortezomib) for Injection
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Dosage and Administration	
Management of Peripheral Neuropathy (2.5)	1/2012
Administration Precautions (2.7)	1/2012
Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)	1/2012
Warnings and Precautions, Peripheral Neuropathy (5.1)	1/2012

----------INDICATIONS AND USAGE----------

VELCADE is a proteasome inhibitor indicated for:

- treatment of patients with multiple myeloma (1.1)
- treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy (1.2)

----------DOSAGE AND ADMINISTRATION----------

The recommended dose of VELCADE is 1.3 mg/m^2 administered either as a 3 to 5 second bolus intravenous injection or subcutaneous injection. (2.1, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- 1 single-use vial contains 3.5 mg of bortezomib. Dose must be individualized to prevent overdose. (3)

----------CONTRAINDICATIONS----------

- VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol. (4)
- VELCADE is contraindicated for intrathecal administration. (4)

----------WARNINGS AND PRECAUTIONS----------

- Peripheral neuropathy, including severe cases, may occur - manage with dose modification or discontinuation. (2.5) Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment. (2.5, 5.1)
- Hypotension can occur. Use caution when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated. (5.2)
- Closely monitor patients with existing heart disease or risk factors for heart disease. (5.3)
- Acute diffuse infiltrative pulmonary disease has been reported. (5.4)
- Nausea, diarrhea, constipation, and vomiting have occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement. (5.6)
- Thrombocytopenia or neutropenia can occur; complete blood counts should be regularly monitored throughout treatment. (5.7)
- Tumor Lysis Syndrome (5.8), Reversible Posterior Leukoencephalopathy Syndrome (5.5), and acute hepatic failure (5.9) have been reported.
- Women should avoid becoming pregnant while being treated with VELCADE. Pregnant women should be apprised of the potential harm to the fetus. (5.11, 8.1)

----------ADVERSE REACTIONS----------

Most commonly reported adverse reactions (incidence ≥ 30%) in clinical studies include asthenic conditions, diarrhea, nausea, constipation, peripheral neuropathy, vomiting, pyrexia, thrombocytopenia, psychiatric disorders, anorexia and decreased appetite, neutropenia, neuralgia, leukopenia and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Millennium Pharmaceuticals at 1-866 VELCADE or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Closely monitor patients receiving VELCADE in combination with strong CYP3A4 inhibitors. (7.1)
- Concomitant use of strong CYP3A4 inducers is not recommended. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Patients with diabetes may require close monitoring of blood glucose and adjustment of anti-diabetic medication. (8.8)
- Hepatic Impairment: Use a lower starting dose for patients with moderate or severe hepatic impairment. (2.6, 5.10, 8.7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [1/2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma.

1.2 Mantle Cell Lymphoma

VELCADE (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

2 DOSAGE AND ADMINISTRATION

The recommended starting dose of VELCADE is 1.3 mg/m^2. VELCADE may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL [*see Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)*]. When administered intravenously, VELCADE is administered as a 3 to 5 second bolus intravenous injection. VELCADE is for intravenous or subcutaneous use only. VELCADE should not be administered by any other route.

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

2.1 Dosage in Previously Untreated Multiple Myeloma

VELCADE (bortezomib) for Injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 1. In Cycles 1-4, VELCADE is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, VELCADE is administered once weekly (days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of VELCADE.

Table 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma

Twice Weekly VELCADE (Cycles 1-4)

Week	**1**				**2**		**3**	**4**		**5**		**6**
VELCADE (1.3 mg/m^2)	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
Melphalan(9 mg/m^2) Prednisone(60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Once Weekly VELCADE (Cycles 5-9 when used in combination with Melphalan and Prednisone)

Week	**1**				**2**		**3**	**4**		**5**		**6**
VELCADE (1.3 mg/m^2)	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan(9 mg/m^2) Prednisone(60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

2.2 Dose Modification Guidelines for Combination Therapy with VELCADE, Melphalan and Prednisone

Prior to initiating any cycle of therapy with VELCADE in combination with melphalan and prednisone:

- Platelet count should be at least 70 x 10^9/L and the absolute neutrophil count (ANC) should be at least 1.0 x 10^9/L
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 2: Dose Modifications during Cycles of Combination VELCADE, Melphalan and Prednisone Therapy

Toxicity	Dose modification or delay
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
If platelet count is not above 30×10^9/L or ANC is not above 0.75×10^9/L on a VELCADE dosing day (other than day 1)	VELCADE dose should be withheld
If several VELCADE doses in consecutive cycles are withheld due to toxicity	VELCADE dose should be reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade 3 or higher non-hematological toxicities	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold or modify VELCADE as outlined in Table 3.

For information concerning melphalan and prednisone, see manufacturer's prescribing information.

For dose modifications guidelines for peripheral neuropathy see Management of Peripheral Neuropathy section (2.5).

2.3 Dosage in Relapsed Multiple Myeloma and Mantle Cell Lymphoma

VELCADE (1.3 mg/m^2/dose) is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, VELCADE may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) [*see Clinical Studies section (14) for a description of dose administration during the trials*]. At least 72 hours should elapse between consecutive doses of VELCADE.

2.4 Dose Modification Guidelines for Relapsed Multiple Myeloma and Mantle Cell Lymphoma

VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below [*see Warnings and Precautions (5)*]. Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

For dose modifications guidelines for peripheral neuropathy see Management of Peripheral Neuropathy section (2.5).

2.5 Management of Peripheral Neuropathy

Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy. Patients with pre-existing severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule.

For dose or schedule modification guidelines for patients who experience VELCADE-related neuropathic pain and/or peripheral neuropathy see Table 3.

Table 3: Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms*	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce VELCADE to 1 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL ***)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue VELCADE

*Grading based on NCI Common Terminology Criteria CTCAE v4.0

**Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc;

***Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

2.6 Dosage in Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELCADE dose. Patients with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance (see Table 4). [*see Warnings and Precautions (5.10), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*]

Table 4: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	Less than or equal to 1.0x ULN	More than ULN	None
	More than 1.0x–1.5x ULN	Any	None
Moderate	More than 1.5x–3x ULN	Any	Reduce VELCADE to 0.7 mg/m^2 in the first cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	More than 3x ULN	Any	

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;
AST = aspartate aminotransferase; ULN = upper limit of the normal range.

2.7 Administration Precautions

The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose. [*see Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)*]

When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

If local injection site reactions occur following VELCADE administration subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously [*see Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)* and follow reconstitution instructions for 1 mg/mL]. Alternatively, the intravenous route of administration should be considered [*see Reconstitution/Preparation for Intravenous and Subcutaneous Administration (2.8)*]

VELCADE is an antineoplastic. Procedures for proper handling and disposal should be considered. [*see How Supplied/Storage and Handling (16)*]

In clinical trials of VELCADE intravenous, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage. In a clinical trial of subcutaneous VELCADE, a local reaction was reported in 6% of patients as an adverse event, mostly redness.

2.8 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

Proper aseptic technique should be used. Reconstitute **only with 0.9% sodium chloride**. The reconstituted product should be a clear and colorless solution.

Different volumes of 0.9% sodium chloride are used to reconstitute the product for the different routes of administration. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). **Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered** [*see Administration Precautions (2.7)*]

For each 3.5 mg single-use vial of bortezomib reconstitute with the following volume of 0.9% sodium chloride based on route of administration (Table 5):

Table 5: Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration

Route of administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib concentration (mg/mL)
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

After determining patient body surface area (BSA) in square meters, use the following equations to calculate the total volume (mL) of reconstituted VELCADE to be administered:

- **Intravenous Administration [1 mg/mL concentration]**

$$\frac{\text{VELCADE dose (mg/m}^2\text{) x patient BSA (m}^2\text{)}}{\text{1 mg/mL}} = \text{Total VELCADE volume (mL) to be administered}$$

- **Subcutaneous Administration [2.5 mg/mL concentration]**

$$\frac{\text{VELCADE dose (mg/m}^2\text{) x patient BSA (m}^2\text{)}}{\text{2.5 mg/mL}} = \text{Total VELCADE volume (mL) to be administered}$$

Stickers that indicate the route of administration are provided with each VELCADE vial. These stickers should be placed directly on the syringe of VELCADE once VELCADE is prepared to help alert practitioners of the correct route of administration for VELCADE.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

Stability: Unopened vials of VELCADE are stable until the date indicated on the package when stored in the original package protected from light.

VELCADE contains no antimicrobial preservative. Reconstituted VELCADE should be administered within 8 hours of preparation. When reconstituted as directed, VELCADE may be stored at 25°C (77°F). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to 8 hours in a syringe; however, total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

3 DOSAGE FORMS AND STRENGTHS

Each single-use vial of VELCADE contains 3.5 mg of bortezomib as a sterile lyophilized powder.

4 CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol.

VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

5 WARNINGS AND PRECAUTIONS

VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy. Complete blood counts (CBC) should be monitored frequently during treatment with VELCADE.

5.1 Peripheral Neuropathy

VELCADE treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing VELCADE subcutaneous vs. intravenous the incidence of Grade ≥ 2 peripheral neuropathy events was 24% for subcutaneous and 41% for intravenous. Grade ≥ 3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 16% in the intravenous treatment group. Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may benefit from a decrease in the dose and/or a less dose-intense schedule [*see Dosage and Administration (2.5)*]. In the single agent phase 3 relapsed multiple myeloma study of VELCADE vs. Dexamethasone following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the relapsed multiple myeloma study. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥ Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies [*see Adverse Reactions (6)*]. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

5.2 Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 13%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics [*see Adverse Reactions (6)*].

5.3 Cardiac Disorders

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the relapsed multiple myeloma study of VELCADE vs. dexamethasone, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the VELCADE and dexamethasone groups, 5% and 4%, respectively. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

5.4 Pulmonary Disorders

There have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving VELCADE. Some of these events have been fatal.

In a clinical trial, the first two patients given high-dose cytarabine ($2g/m^2$ per day) by continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy.

There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease.

In the event of new or worsening cardiopulmonary symptoms, a prompt comprehensive diagnostic evaluation should be conducted.

5.5 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

There have been reports of RPLS in patients receiving VELCADE. RPLS is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing RPLS, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing RPLS is not known.

5.6 Gastrointestinal Adverse Events

VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting [*see Adverse Reactions (6)*] sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration.

5.7 Thrombocytopenia/Neutropenia

VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pretreatment platelet count is shown in Table 6. In the relapsed multiple myeloma study of VELCADE vs. dexamethasone, the incidence of significant bleeding events (≥ Grade 3) was similar on both the

VELCADE (4%) and dexamethasone (5%) arms. Platelet count should be monitored prior to each dose of VELCADE. Patients experiencing thrombocytopenia may require change in the dose and schedule of VELCADE [*see Table 2 and Dosage and Administration (2.4)*]. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE. Transfusions may be considered. The incidence of febrile neutropenia was < 1%.

Table 6: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Relapsed Multiple Myeloma Study of VELCADE vs. Dexamethasone

Pretreatment Platelet Count*	Number of Patients (N=331)**	Number (%) of Patients with Platelet Count < 10,000/μL	Number (%) of Patients with Platelet Count 10,000-25,000/μL
≥ 75,000/μL	309	8 (3%)	36 (12%)
≥ 50,000/μL- < 75,000/μL	14	2 (14%)	11 (79%)
≥ 10,000/μL- < 50,000/μL	7	1 (14%)	5 (71%)

* A baseline platelet count of 50,000/μL was required for study eligibility
** Data were missing at baseline for 1 patient

5.8 Tumor Lysis Syndrome

Because VELCADE is a cytotoxic agent and can rapidly kill malignant cells, the complications of tumor lysis syndrome may occur. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

5.9 Hepatic Events

Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic events include increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of VELCADE. There is limited re-challenge information in these patients.

5.10 Hepatic Impairment

Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with VELCADE at reduced starting doses and closely monitored for toxicities. [*see Dosage and Administration (2.6), Use In Specific Populations (8.7) and Clinical Pharmacology (12.3)*]

5.11 Use in Pregnancy

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses. [*see Use in Specific Populations (8.1)*]

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Peripheral Neuropathy [*see Warnings and Precautions (5.1); Dosage and Administration (2.5)(Table 3)*]
- Hypotension [*see Warnings and Precautions (5.2)*]
- Cardiac Disorders [*see Warnings and Precautions (5.3)*]
- Pulmonary Disorders [*see Warnings and Precautions (5.4)*]
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [*see Warnings and Precautions (5.5)*]

- Gastrointestinal Adverse Events [*see Warnings and Precautions (5.6)*]
- Thrombocytopenia/Neutropenia [*see Warnings and Precautions (5.7)*]
- Tumor Lysis Syndrome [*see Warnings and Precautions (5.8)*]
- Hepatic Events [*see Warnings and Precautions (5.9)*]

6.1 Clinical Trials Safety Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Summary of Clinical Trial in Patients with Previously Untreated Multiple Myeloma:

Table 7 describes safety data from 340 patients with previously untreated multiple myeloma who received VELCADE (1.3 mg/m^2) administered intravenously in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective randomized study.

The safety profile of VELCADE in combination with melphalan/prednisone is consistent with the known safety profiles of both VELCADE and melphalan/prednisone.

Table 7: Most Commonly Reported Adverse Events (≥ 10% in VELCADE, Melphalan and Prednisone arm) with Grades 3 and ≥ 4 Intensity in the Previously Untreated Multiple Myeloma Study

	VELCADE, Melphalan and Prednisone (N=340)			**Melphalan and Prednisone** (N=337)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Blood and Lymphatic System Disorders						
Thrombocytopenia	178 (52)	68 (20)	59 (17)	159 (47)	55 (16)	47 (14)
Neutropenia	165 (49)	102 (30)	35 (10)	155 (46)	79 (23)	49 (15)
Anemia	147 (43)	53 (16)	9 (3)	187 (55)	66 (20)	26 (8)
Leukopenia	113 (33)	67 (20)	10 (3)	100 (30)	55 (16)	13 (4)
Lymphopenia	83 (24)	49 (14)	18 (5)	58 (17)	30 (9)	7 (2)
Gastrointestinal Disorders						
Nausea	164 (48)	14 (4)	0	94 (28)	1 (<1)	0
Diarrhea	157 (46)	23 (7)	2 (1)	58 (17)	2 (1)	0
Constipation	125 (37)	2 (1)	0	54 (16)	0	0
Vomiting	112 (33)	14 (4)	0	55 (16)	2 (1)	0
Abdominal Pain	49 (14)	7 (2)	0	22 (7)	1 (<1)	0
Abdominal Pain Upper	40 (12)	1 (<1)	0	29 (9)	0	0
Dyspepsia	39 (11)	0	0	23 (7)	0	0
Nervous System Disorders						
Peripheral Neuropathy	159 (47)	43 (13)	2 (1)	18 (5)	0	0
Neuralgia	121 (36)	28 (8)	2 (1)	5 (1)	1 (<1)	0
Dizziness	56 (16)	7 (2)	0	37 (11)	1 (<1)	0
Headache	49 (14)	2 (1)	0	35 (10)	4 (1)	0
Paresthesia	45 (13)	6 (2)	0	15 (4)	0	0

General Disorders and Administration Site Conditions						
Pyrexia	99 (29)	8 (2)	2 (1)	64 (19)	6 (2)	2 (1)
Fatigue	98 (29)	23 (7)	2 (1)	86 (26)	7 (2)	0
Asthenia	73 (21)	20 (6)	1 (<1)	60 (18)	9 (3)	0
Edema Peripheral	68 (20)	2 (1)	0	34 (10)	0	0
Infections and Infestations						
Pneumonia	56 (16)	16 (5)	13 (4)	36 (11)	13 (4)	9 (3)
Herpes Zoster	45 (13)	11 (3)	0	14 (4)	6 (2)	0
Bronchitis	44 (13)	4 (1)	0	27 (8)	4 (1)	0
Nasopharyngitis	39 (11)	1 (<1)	0	27 (8)	0	0
Musculoskeletal and Connective Tissue Disorders						
Back Pain	58 (17)	9 (3)	1 (<1)	62 (18)	11 (3)	1 (<1)
Pain In Extremity	47 (14)	8 (2)	0	32 (9)	3 (1)	1 (<1)
Bone Pain	37 (11)	7 (2)	1 (<1)	35 (10)	7 (2)	0
Arthralgia	36 (11)	4 (1)	0	50 (15)	2 (1)	1 (<1)
Metabolism and Nutrition Disorders						
Anorexia	77 (23)	9 (3)	1 (<1)	34 (10)	4 (1)	0
Hypokalemia	44 (13)	19 (6)	3 (1)	25 (7)	8 (2)	2 (1)
Skin and Subcutaneous Tissue Disorders						
Rash	66 (19)	2 (1)	0	24 (7)	1 (<1)	0
Pruritus	35 (10)	3 (1)	0	18 (5)	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	71 (21)	0	0	45 (13)	2 (1)	0
Dyspnea	50 (15)	11 (3)	2 (1)	44 (13)	5 (1)	4 (1)
Psychiatric Disorders						
Insomnia	69 (20)	1 (<1)	0	43 (13)	0	0
Vascular Disorders						
Hypertension	45 (13)	8 (2)	1 (<1)	25 (7)	2 (1)	0
Hypotension	41 (12)	4 (1)	3 (1)	10 (3)	2 (1)	2 (1)

Relapsed Multiple Myeloma Randomized Study of VELCADE vs. Dexamethasone

The safety data described below and in Table 8 reflect exposure to either VELCADE (n=331) or dexamethasone (n=332) in a study of patients with relapsed multiple myeloma. VELCADE was administered intravenously at doses of 1.3 mg/m^2 twice weekly for 2 out of 3 weeks (21 day cycle). After eight 21-day cycles patients continued therapy for three 35-day cycles on a weekly schedule. Duration of treatment was up to 11 cycles (9 months) with a median duration of 6 cycles (4.1 months). For inclusion in the trial, patients must have had measurable disease and 1 to 3 prior therapies. There was no upper age limit for entry. Creatinine clearance could be as low as 20 mL/min and bilirubin levels as high as 1.5 times the upper limit of normal. The overall frequency of adverse events was similar in men and women, and in patients < 65 and ≥ 65 years of age. Most patients were Caucasian. [*see Clinical Studies (14.1)*]

Among the 331 VELCADE-treated patients, the most commonly reported events overall were asthenic conditions (61%), diarrhea and nausea (each 57%), constipation (42%), peripheral neuropathy NEC (36%), vomiting, pyrexia, thrombocytopenia, and psychiatric disorders (each 35%), anorexia and appetite decreased (34%), paresthesia and dysesthesia (27%), anemia and headache (each 26%), and cough (21%). The most commonly reported adverse events reported among the 332 patients in the dexamethasone group were psychiatric disorders (49%), asthenic conditions (45%), insomnia (27%), anemia (22%), and diarrhea and lower respiratory/lung infections (each 21%). Fourteen percent (14%) of patients in the VELCADE treated arm experienced a Grade 4 adverse event; the most common toxicities were thrombocytopenia (4%), neutropenia (2%) and hypercalcemia (2%). Sixteen percent (16%) of dexamethasone treated patients experienced a Grade 4 adverse event; the most common toxicity was hyperglycemia (2%).

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of VELCADE vs. Dexamethasone

Serious adverse events are defined as any event, regardless of causality, that results in death, is life-threatening, requires hospitalization or prolongs a current hospitalization, results in a significant disability, or is deemed to be an important medical event. A total of 144 (44%) patients from the VELCADE treatment arm experienced an SAE during the study, as did 144 (43%) dexamethasone-treated patients. The most commonly reported SAEs in the VELCADE treatment arm were pyrexia (6%), diarrhea (5%), dyspnea and pneumonia (4%), and vomiting (3%). In the dexamethasone treatment group, the most commonly reported SAEs were pneumonia (7%), pyrexia (4%), and hyperglycemia (3%).

A total of 145 patients, including 84 (25%) of 331 patients in the VELCADE treatment group and 61 (18%) of 332 patients in the dexamethasone treatment group were discontinued from treatment due to adverse events assessed as drug-related by the investigators. Among the 331 VELCADE treated patients, the most commonly reported drug-related event leading to discontinuation was peripheral neuropathy (8%). Among the 332 patients in the dexamethasone group, the most commonly reported drug-related events leading to treatment discontinuation were psychotic disorder and hyperglycemia (2% each).

Four deaths were considered to be VELCADE related in this relapsed multiple myeloma study: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four deaths were considered dexamethasone-related: 2 cases of sepsis, 1 case of bacterial meningitis, and 1 case of sudden death at home.

Most Commonly Reported Adverse Events in the Relapsed Multiple Myeloma Study of VELCADE vs. Dexamethasone

The most common adverse events from the relapsed multiple myeloma study are shown in Table 8. All adverse events with incidence ≥ 10% in the VELCADE arm are included.

Table 8: Most Commonly Reported Adverse Events (≥ 10% in VELCADE arm), with Grades 3 and 4 Intensity in the Relapsed Multiple Myeloma Study of VELCADE vs. Dexamethasone (N=663)

	Treatment Group					
	VELCADE (n=331) [n (%)]			Dexamethasone (n=332) [n (%)]		
	All Events	Grade 3 Events	Grade 4 Events	All Events	Grade 3 Events	Grade 4 Events
Adverse Event	331 (100)	203 (61)	45 (14)	327 (98)	146 (44)	52 (16)
Asthenic conditions	201 (61)	39 (12)	1 (<1)	148 (45)	20 (6)	0
Diarrhea	190 (57)	24 (7)	0	69 (21)	6 (2)	0
Nausea	190 (57)	8 (2)	0	46 (14)	0	0
Constipation	140 (42)	7 (2)	0	49 (15)	4 (1)	0
Peripheral neuropathy	120 (36)	24 (7)	2 (<1)	29 (9)	1 (<1)	1 (<1)
Vomiting	117 (35)	11 (3)	0	20 (6)	4 (1)	0
Pyrexia	116 (35)	6 (2)	0	54 (16)	4 (1)	1 (<1)
Thrombocytopenia	115 (35)	85 (26)	12 (4)	36 (11)	18 (5)	4 (1)
Psychiatric disorders	117 (35)	9 (3)	2 (<1)	163 (49)	26 (8)	3 (<1)
Anorexia and appetite decreased	112 (34)	9 (3)	0	31 (9)	1 (<1)	0
Paresthesia and dysesthesia	91 (27)	6 (2)	0	38 (11)	1 (<1)	0
Anemia	87 (26)	31 (9)	2 (<1)	74 (22)	32 (10)	3 (<1)
Headache	85 (26)	3 (<1)	0	43 (13)	2 (<1)	0
Cough	70 (21)	2 (<1)	0	35 (11)	1 (<1)	0
Dyspnea	65 (20)	16 (5)	1 (<1)	58 (17)	9 (3)	2 (<1)
Neutropenia	62 (19)	40 (12)	8 (2)	5 (2)	4 (1)	0
Rash	61 (18)	4 (1)	0	20 (6)	0	0
Insomnia	60 (18)	1 (<1)	0	90 (27)	5 (2)	0
Abdominal pain	53 (16)	6 (2)	0	12 (4)	1 (<1)	0
Bone pain	52 (16)	12 (4)	0	50 (15)	9 (3)	0
Lower respiratory/ lung infections	48 (15)	12 (4)	2 (<1)	69 (21)	24 (7)	1 (<1)
Pain in limb	50 (15)	5 (2)	0	24 (7)	2 (<1)	0
Back pain	46 (14)	10 (3)	0	33 (10)	4 (1)	0
Arthralgia	45 (14)	3 (<1)	0	35 (11)	5 (2)	0
Dizziness (excl. vertigo)	45 (14)	3 (<1)	0	34 (10)	0	0
Nasopharyngitis	45 (14)	1 (<1)	0	22 (7)	0	0
Herpes zoster	42 (13)	6 (2)	0	15 (5)	4 (1)	1 (<1)
Muscle cramps	41 (12)	0	0	50 (15)	3 (<1)	0
Myalgia	39 (12)	1 (<1)	0	18 (5)	1 (<1)	0
Rigors	37 (11)	0	0	8 (2)	0	0
Edema lower limb	35 (11)	0	0	43 (13)	1 (<1)	0

Safety Experience from the Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma

In the phase 2 extension study of 63 patients, no new cumulative or new long-term toxicities were observed with prolonged VELCADE treatment. These patients were treated for a total of 5.3 to 23 months, including time on VELCADE in the prior VELCADE study. [*see Clinical Studies (14)*]

Safety Experience from the Phase 3 Open-Label Study of VELCADE Subcutaneous vs. Intravenous in Relapsed Multiple Myeloma

The safety and efficacy of VELCADE administered subcutaneously were evaluated in one Phase 3 study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of VELCADE subcutaneous vs. intravenous in 222 patients with relapsed multiple myeloma. The safety data described below and in Table 9 reflect exposure to either VELCADE subcutaneous (n=147) or VELCADE intravenous (n=74) [*see Clinical Studies (14.1)*]

Table 9: Most Commonly Reported Adverse Events (≥ 10%), with Grade 3 and ≥ 4 Intensity in the Relapsed Multiple Myeloma Study (N=221) of VELCADE Subcutaneous vs. Intravenous

	Subcutaneous (N=147)[a]			Intravenous (N=74)[a]		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
MedDRA Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Blood and lymphatic system disorders						
Anaemia	53 (36)	14 (10)	4 (3)	26 (35)	6 (8)	0
Leukopenia	29 (20)	9 (6)	0	16 (22)	4 (5)	1 (1)
Neutropenia	42 (29)	22 (15)	4 (3)	20 (27)	10 (14)	3 (4)
Thrombocytopenia	52 (35)	12 (8)	7 (5)	27 (36)	8 (11)	6 (8)
Gastrointestinal disorders						
Abdominal pain	5 (3)	1 (1)	0	8 (11)	0	0
Abdominal pain upper	3 (2)	0	0	8 (11)	0	0
Constipation	21 (14)	1 (1)	0	11 (15)	1 (1)	0
Diarrhea	35 (24)	2 (1)	1 (1)	27 (36)	3 (4)	1 (1)
Nausea	27 (18)	0	0	14 (19)	0	0
Vomiting	17 (12)	3 (2)	0	12 (16)	0	1 (1)
General disorders and administration site conditions						
Asthenia	23 (16)	3 (2)	0	14 (19)	4 (5)	0
Fatigue	17 (12)	3 (2)	0	15 (20)	3 (4)	0
Pyrexia	28 (19)	0	0	12 (16)	0	0
Infections and infestations						
Herpes zoster	16 (11)	2 (1)	0	7 (9)	1 (1)	0
Investigations						
Weight decreased	22 (15)	0	0	2 (3)	1 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	14 (10)	0	0	7 (9)	0	0
Musculoskeletal and connective tissue disorders						
Back pain	21 (14)	1 (1)	0	8 (11)	1 (1)	1 (1)
Pain in extremity	8 (5)	1 (1)	0	8 (11)	2 (3)	0
Nervous system disorders						
Headache	5 (3)	0	0	8 (11)	0	0
Neuralgia	35 (24)	5 (3)	0	17 (23)	7 (9)	0
Peripheral neuropathies NEC[b]	56 (38)	8 (5)	1 (1)	39 (53)	11 (15)	1 (1)
Psychiatric disorders						
Insomnia	18 (12)	0	0	8 (11)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	11 (7)	2 (1)	0	9 (12)	2 (3)	0
Vascular disorders						
Hypertension	14 (10)	3 (2)	0	3 (4)	0	0

[a] Safety population: 147 patients in the subcutaneous treatment and 74 patients in the intravenous treatment who received at least 1 dose of study medication

[b] Represents MedDRA high level term

In general, safety data were similar for the subcutaneous and intravenous treatment groups. Differences were observed in the rates of some Grade ≥ 3 adverse events. Differences of ≥ 5% were reported in neuralgia (3%

subcutaneous vs. 9% intravenous), peripheral neuropathy (6% subcutaneous vs. 16% intravenous), and thrombocytopenia (14% subcutaneous vs. 19% intravenous).

A local reaction was reported in 6% of patients in the subcutaneous group as an adverse event, mostly redness. Only 2 (1%) patients were reported as having severe reactions, 1 case of pruritus and 1 case of redness. Local reactions led to reduction in injection concentration in one patient and drug discontinuation in one patient. Local reaction events resolved in a median of 6 days.

Dose reductions occurred due to drug related adverse events in 31% of patients in the subcutaneous treatment group compared with 43% of the intravenously treated patients. The most common adverse events leading to a dose reduction included peripheral sensory neuropathy (17% in the subcutaneous treatment group compared with 31% in the intravenous treatment group); and neuralgia (11% in the subcutaneous treatment group compared with 19% in the intravenous treatment group).

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs. Intravenous

The incidence of serious adverse events was similar for the subcutaneous treatment group (36%) and the intravenous treatment group (35%). The most commonly reported SAEs in the subcutaneous treatment arm were pneumonia (6%) and pyrexia (3%). In the intravenous treatment group, the most commonly reported SAEs were pneumonia (7%), diarrhea (4%), peripheral sensory neuropathy (3%) and renal failure (3%).

In the subcutaneous treatment group, 27 patients (18%) discontinued study treatment due to a drug related adverse event compared with 17 patients (23%) in the intravenous treatment group. Among the 147 subcutaneously treated patients, the most commonly reported drug-related event leading to discontinuation was peripheral sensory neuropathy (5%) and neuralgia (5%). Among the 74 patients in the intravenous treatment group, the most commonly reported drug-related events leading to treatment discontinuation were peripheral sensory neuropathy (9%) and neuralgia (9%).

Two patients (1%) in the subcutaneous treatment group and 1 (1%) patient in the intravenous treatment group died due to a drug-related adverse event during treatment. In the subcutaneous group the causes of death were one case of pneumonia and one of sudden death. In the intravenous group the cause of death was coronary artery insufficiency.

Integrated Summary of Safety (Relapsed Multiple Myeloma and Mantle Cell Lymphoma)

Safety data from phase 2 and 3 studies of single agent VELCADE 1.3 mg/m^2/dose twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with previously treated multiple myeloma (N=1008) and previously treated mantle cell lymphoma (N=155) were integrated and tabulated. This analysis does not include data from the Phase 3 Open-Label Study of VELCADE subcutaneous vs. intravenous in relapsed multiple myeloma. In the integrated studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma. [*see Clinical Studies (14)*]

In the integrated analysis, the most commonly reported adverse events were asthenic conditions (including fatigue, malaise, and weakness) (64%), nausea (55%), diarrhea (52%), constipation (41%), peripheral neuropathy NEC (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (39%), thrombocytopenia and appetite decreased (including anorexia) (each 36%), pyrexia (34%), vomiting (33%), and anemia (29%). Twenty percent (20%) of patients experienced at least 1 episode of ≥ Grade 4 toxicity, most commonly thrombocytopenia (5%) and neutropenia (3%).

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Integrated Summary of Safety

A total of 50% of patients experienced SAEs during the studies. The most commonly reported SAEs included pneumonia (7%), pyrexia (6%), diarrhea (5%), vomiting (4%), and nausea, dehydration, dyspnea and thrombocytopenia (each 3%).

Adverse events thought by the investigator to be drug-related and leading to discontinuation occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy (8%), asthenic conditions (3%) and thrombocytopenia and diarrhea (each 2%).

In total, 2% of the patients died and the cause of death was considered by the investigator to be possibly related to study drug: including reports of cardiac arrest, congestive heart failure, respiratory failure, renal failure, pneumonia and sepsis.

Most Commonly Reported Adverse Events in the Integrated Summary of Safety

The most common adverse events are shown in Table 10. All adverse events occurring at ≥ 10% are included. In the absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are drug-caused and those that reflect the patient's underlying disease. Please see the discussion of specific adverse reactions that follows.

Table 10: Most Commonly Reported (≥ 10% Overall) Adverse Events in Integrated Analyses of Relapsed Multiple Myeloma and Mantle Cell Lymphoma Studies using the 1.3 mg/m^2 Dose (N=1163)

	All Patients (N=1163)		Multiple Myeloma (N=1008)		Mantle Cell Lymphoma (N=155)	
Adverse Events	**All Events**	**≥ Grade 3**	**All Events**	**≥ Grade 3**	**All Events**	**≥ Grade 3**
Asthenic conditions	740 (64)	189 (16)	628 (62)	160 (16)	112 (72)	29 (19)
Nausea	640 (55)	43 (4)	572 (57)	39 (4)	68 (44)	4 (3)
Diarrhea	604 (52)	96 (8)	531 (53)	85 (8)	73 (47)	11 (7)
Constipation	481 (41)	26 (2)	404 (40)	22 (2)	77 (50)	4 (3)
Peripheral neuropathy	457 (39)	134 (12)	372 (37)	114 (11)	85 (55)	20 (13)
Thrombocytopenia	421 (36)	337 (29)	388 (38)	320 (32)	33 (21)	17 (11)
Appetite decreased	417 (36)	30 (3)	357 (35)	25 (2)	60 (39)	5 (3)
Pyrexia	401 (34)	36 (3)	371 (37)	34 (3)	30 (19)	2 (1)
Vomiting	385 (33)	57 (5)	343 (34)	53 (5)	42 (27)	4 (3)
Anemia	333 (29)	124 (11)	306 (30)	120 (12)	27 (17)	4 (3)
Edema	262 (23)	10 (<1)	218 (22)	6 (<1)	44 (28)	4 (3)
Paresthesia and dysesthesia	254 (22)	16 (1)	240 (24)	14 (1)	14 (9)	2 (1)
Headache	253 (22)	17 (1)	227 (23)	17 (2)	26 (17)	0
Dyspnea	244 (21)	59 (5)	209 (21)	52 (5)	35 (23)	7 (5)
Cough	232 (20)	5 (<1)	202 (20)	5 (<1)	30 (19)	0
Insomnia	232 (20)	7 (<1)	199 (20)	6 (<1)	33 (21)	1 (<1)
Rash	213 (18)	10 (<1)	170 (17)	6 (<1)	43 (28)	4 (3)
Arthralgia	199 (17)	27 (2)	179 (18)	25 (2)	20 (13)	2 (1)
Neutropenia	195 (17)	143 (12)	185 (18)	137 (14)	10 (6)	6 (4)
Dizziness (excluding vertigo)	195 (17)	18 (2)	159 (16)	13 (1)	36 (23)	5 (3)
Pain in limb	179 (15)	36 (3)	172 (17)	36 (4)	7 (5)	0
Abdominal pain	170 (15)	30 (3)	146 (14)	22 (2)	24 (15)	8 (5)
Bone pain	166 (14)	37 (3)	163 (16)	37 (4)	3 (2)	0
Back pain	151 (13)	39 (3)	150 (15)	39 (4)	1 (<1)	0
Hypotension	147 (13)	37 (3)	124 (12)	32 (3)	23 (15)	5 (3)
Herpes zoster	145 (12)	22 (2)	131 (13)	21 (2)	14 (9)	1 (<1)
Nasopharyngitis	139 (12)	2 (<1)	126 (13)	2 (<1)	13 (8)	0
Upper respiratory tract infection	138 (12)	2 (<1)	114 (11)	1 (<1)	24 (15)	1 (<1)
Myalgia	136 (12)	9 (<1)	121 (12)	9 (<1)	15 (10)	0
Pneumonia	134 (12)	72 (6)	120 (12)	65 (6)	14 (9)	7 (5)
Muscle cramps	125 (11)	1 (<1)	118 (12)	1 (<1)	7 (5)	0
Dehydration	120 (10)	40 (3)	109 (11)	33 (3)	11 (7)	7 (5)
Anxiety	118 (10)	6 (<1)	111 (11)	6 (<1)	7 (5)	0

Description of Selected Adverse Events from the Integrated Phase 2 and 3 Relapsed Multiple Myeloma and Phase 2 Mantle Cell Lymphoma Studies

Gastrointestinal Events

A total of 87% of patients experienced at least one GI disorder. The most common GI disorders included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other GI disorders included dyspepsia and dysgeusia. Grade 3 GI events occurred in 18% of patients; Grade 4 events were 1%. GI events were considered serious in 11% of patients. Five percent (5%) of patients discontinued due to a GI event. Nausea was reported more often in patients with multiple myeloma (57%) compared to patients with mantle cell lymphoma (44%). [*see Warnings and Precautions (5.6)*]

Thrombocytopenia

Across the studies, VELCADE associated thrombocytopenia was characterized by a decrease in platelet count during the dosing period (days 1 to 11) and a return toward baseline during the 10-day rest period during each treatment cycle. Overall, thrombocytopenia was reported in 36% of patients. Thrombocytopenia was Grade 3 in 24%, ≥ Grade 4 in 5%, and serious in 3% of patients, and the event resulted in VELCADE discontinuation in 2% of patients [*see Warnings and Precautions (5.7)*]. Thrombocytopenia was reported more often in patients with multiple myeloma (38%) compared to patients with mantle cell lymphoma (21%). The incidence of ≥ Grade 3 thrombocytopenia also was higher in patients with multiple myeloma (32%) compared to patients with mantle cell lymphoma (11%). [*see Warnings and Precautions (5.7)*]

Peripheral Neuropathy

Overall, peripheral neuropathy NEC occurred in 39% of patients. Peripheral neuropathy was Grade 3 for 11% of patients and Grade 4 for < 1% of patients. Eight percent (8%) of patients discontinued VELCADE due to peripheral neuropathy. The incidence of peripheral neuropathy was higher among patients with mantle cell lymphoma (55%) compared to patients with multiple myeloma (37%).

In the relapsed multiple myeloma study, among the 87 patients who experienced ≥ Grade 2 peripheral neuropathy, 51% had improved or resolved with a median of 3.5 months from first onset.

Among the patients with peripheral neuropathy in the phase 2 multiple myeloma studies that was Grade 2 and led to discontinuation or was ≥ Grade 3, 73% (24 of 33) reported improvement or resolution following VELCADE dose adjustment, with a median time to improvement of one Grade or more from the last dose of VELCADE of 33 days. [*see Warnings and Precautions (5.1)*]

Hypotension

The incidence of hypotension (postural hypotension, orthostatic hypotension and hypotension NOS) was 13% in patients treated with VELCADE. Hypotension was Grade 1 or 2 in the majority of patients and Grade 3 in 3% and ≥ Grade 4 in < 1%. Three percent (3%) of patients had hypotension reported as an SAE, and 1% discontinued due to hypotension. The incidence of hypotension was similar in patients with multiple myeloma (12%) and those with mantle cell lymphoma (15%). In addition, 2% of patients experienced hypotension and had a syncopal event. Doses of antihypertensive medications may need to be adjusted in patients receiving VELCADE. [*see Warnings and Precautions (5.2)*]

Neutropenia

Neutrophil counts decreased during the VELCADE dosing period (days 1 to 11) and returned toward baseline during the 10-day rest period during each treatment cycle. Overall, neutropenia occurred in 17% of patients and was Grade 3 in 9% of patients and ≥ Grade 4 in 3%. Neutropenia was reported as a serious event in < 1% of patients and < 1% of patients discontinued due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma (18%) compared to patients with mantle cell lymphoma (6%). The incidence of ≥ Grade 3 neutropenia also was higher in patients with multiple myeloma (14%) compared to patients with mantle cell lymphoma (4%). [*see Warnings and Precautions (5.7)*]

Asthenic conditions (Fatigue, Malaise, Weakness)
Asthenic conditions were reported in 64% of patients. Asthenia was Grade 3 for 16% and ≥ Grade 4 in < 1% of patients. Four percent (4%) of patients discontinued treatment due to asthenia. Asthenic conditions were reported in 62% of patients with multiple myeloma and 72% of patients with mantle cell lymphoma.

Pyrexia
Pyrexia (> 38°C) was reported as an adverse event for 34% of patients. The event was Grade 3 in 3% and ≥ Grade 4 in < 1%. Pyrexia was reported as a serious adverse event in 6% of patients and led to VELCADE discontinuation in < 1% of patients. The incidence of pyrexia was higher among patients with multiple myeloma (37%) compared to patients with mantle cell lymphoma (19%). The incidence of ≥ Grade 3 pyrexia was 3% in patients with multiple myeloma and 1% in patients with mantle cell lymphoma.

Herpes Virus Infection
Physicians should consider using antiviral prophylaxis in subjects being treated with VELCADE. In the randomized studies in previously untreated and relapsed multiple myeloma, herpes zoster reactivation was more common in subjects treated with VELCADE (13%) than in the control groups (4-5%). Herpes simplex was seen in 2-8% in subjects treated with VELCADE and 1-5% in the control groups. In the previously untreated multiple myeloma study, herpes zoster virus reactivation in the VELCADE, melphalan and prednisone arm was less common in subjects receiving prophylactic antiviral therapy (3%) than in subjects who did not receive prophylactic antiviral therapy (17%). In the postmarketing experience, rare cases of herpes meningoencephalitis and ophthalmic herpes have been reported.

Additional Adverse Events from Clinical Studies

The following clinically important SAEs that are not described above have been reported in clinical trials in patients treated with VELCADE administered as monotherapy or in combination with other chemotherapeutics. These studies were conducted in patients with hematological malignancies and in solid tumors.

Blood and lymphatic system disorders: Disseminated intravascular coagulation, lymphopenia, leukopenia

Cardiac disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, *Torsades de pointes*, ventricular tachycardia

Ear and labyrinth disorders: Hearing impaired, vertigo

Eye disorders: Diplopia and blurred vision, conjunctival infection, irritation

Gastrointestinal disorders: Ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal reflux

General disorders and administration site conditions: Injection site erythema, neuralgia, injection site pain, irritation, phlebitis

Hepatobiliary disorders: Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein thrombosis, hepatitis, liver failure

Immune system disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema

Infections and infestations: Aspergillosis, bacteremia, urinary tract infection, herpes viral infection, listeriosis, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related infection

Injury, poisoning and procedural complications: Catheter related complication, skeletal fracture, subdural hematoma

Metabolism and nutrition disorders: Hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia

Nervous system disorders: Ataxia, coma, dysarthria, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack

Psychiatric disorders: Agitation, confusion, mental status change, psychotic disorder, suicidal ideation

Renal and urinary disorders: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure (acute and chronic), glomerular nephritis proliferative

Respiratory, thoracic and mediastinal disorders: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, pulmonary hypertension

Skin and subcutaneous tissue disorders: Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis

Vascular disorders: Cerebrovascular accident, cerebral hemorrhage, deep venous thrombosis, peripheral embolism, pulmonary embolism, pulmonary hypertension

6.2 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide postmarketing experience with VELCADE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: atrioventricular block complete, cardiac tamponade, ischemic colitis, encephalopathy, dysautonomia, deafness bilateral, disseminated intravascular coagulation, hepatitis, acute pancreatitis, acute diffuse infiltrative pulmonary disease, reversible posterior leukoencephalopathy syndrome, toxic epidermal necrolysis, acute febrile neutrophilic dermatosis (Sweet's syndrome), herpes meningoencephalitis, optic neuropathy, blindness and ophthalmic herpes.

7 DRUG INTERACTIONS

Bortezomib is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2.

7.1 CYP3A4 inhibitors: Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

7.2 CYP2C19 inhibitors: Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients.

7.3 CYP3A4 inducers: Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur.

Efficacy may be reduced when VELCADE is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving VELCADE.

St. John's Wort (*Hypericum perforatum*) may decrease bortezomib exposure unpredictably and should be avoided.

7.4 Dexamethasone: Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients.

7.5 Melphalan-Prednisone: Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.11)*]

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m^2 in the rat and 0.05 mg/kg; 0.6 mg/m^2 in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m^2 based on body surface area.

Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6 mg/m^2) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area.

There are no adequate and well-controlled studies in pregnant women. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VELCADE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of VELCADE in children have not been established.

8.5 Geriatric Use

Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the VELCADE arm and 120 (36%) on the dexamethasone arm. Median time to progression and median duration of response for patients ≥ 65 were longer on VELCADE compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively]. On the VELCADE arm, 40% (n=46) of evaluable patients aged ≥ 65 experienced response (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for VELCADE patients ≤ 50, 51-64 and ≥ 65 years old, respectively. [*see Adverse Reactions (6.1); Clinical Studies (14)*]

No overall differences in safety or effectiveness were observed between patients ≥ age 65 and younger patients receiving VELCADE; but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Renal Impairment

The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing adjustments of VELCADE are not necessary for patients with renal insufficiency. Since dialysis may reduce VELCADE concentrations, VELCADE should be administered after the dialysis procedure. For information concerning dosing of melphalan in patients with renal impairment see manufacturer's prescribing information. [*see Clinical Pharmacology (12.3)*]

8.7 Patients with Hepatic Impairment

The exposure of bortezomib is increased in patients with moderate and severe hepatic impairment. Starting dose should be reduced in those patients. [*see Dosage and Administration (2.6), Warnings and Precautions (5.10), and Pharmacokinetics (12.3)*]

8.8 Patients with Diabetes

During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

10 OVERDOSAGE

There is no known specific antidote for VELCADE overdosage [*see Warnings and Precautions (5) and Dosage and Administration (2)*]. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension (5.2) and thrombocytopenia (5.7). In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given.

Studies in monkeys and dogs showed that intravenous bortezomib doses as low as 2 times the recommended clinical dose on a mg/m^2 basis were associated with increases in heart rate, decreases in contractility, hypotension, and death. In dog studies, a slight increase in the corrected QT interval was observed at doses resulting in death. In monkeys, doses of 3.0 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at 1 hour post-administration, with progression to death in 12 to 14 hours following drug administration.

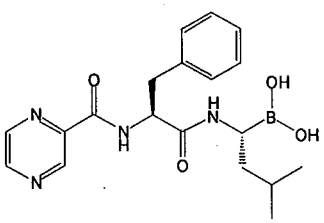
11 DESCRIPTION

VELCADE® (bortezomib) for Injection is an antineoplastic agent available for intravenous injection or subcutaneous use. Each single use vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP.

Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is $C_{19}H_{25}BN_4O_4$. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models, including multiple myeloma.

12.2 Pharmacodynamics

Following twice weekly administration of 1 mg/m^2 and 1.3 mg/m^2 bortezomib doses (n=12 per each dose level), the maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed 5 minutes after drug administration. Comparable maximum inhibition of 20S proteasome activity was observed between 1 and 1.3 mg/m^2 doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m^2 and 1.3 mg/m^2 dose regimens, respectively.

12.3 Pharmacokinetics

Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3mg/m^2 dose. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m^2, respectively.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients (n = 14 for intravenous, n = 17 for subcutaneous) with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administration. The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than intravenous (223 ng/mL). The AUC_{last} geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.

Distribution: The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3mg/m^2 to patients with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

Metabolism: *In vitro* studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form 2 deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination: The pathways of elimination of bortezomib have not been characterized in humans.

Age: Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients who had received intravenous doses of 1 mg/m^2 and 1.3 mg/m^2 showed that both dose-normalized AUC and C_{max} tend to be less in younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and C_{max} than those ≥ 65 years of age (n=13).

Gender: Mean dose-normalized AUC and C_{max} values were comparable between male (n=22) and female (n=17) patients after the first dose of Cycle 1 for the 1 and 1.3 mg/m^2 doses.

Race: The effect of race on exposure to bortezomib could not be assessed as most of the patients were Caucasian.

Hepatic Impairment: The effect of hepatic impairment (see Table 4 for definition of hepatic impairment) on the pharmacokinetics of bortezomib was assessed in 51 cancer patients at bortezomib doses ranging from 0.5 to 1.3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by

approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely. [*see Dosage and Administration (2.6), Warnings and Precautions (5.10) and Use in Specific Populations (8.7)*]

Renal Impairment: A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCl) into the following groups: Normal (CrCl ≥60 mL/min/1.73 m^2, N=12), Mild (CrCl=40-59 mL/min/1.73 m^2, N=10), Moderate (CrCl=20-39 mL/min/1.73 m^2, N=9), and Severe (CrCl < 20 mL/min/1.73 m^2, N=3). A group of dialysis patients who were dosed after dialysis was also included in the study (N=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C_{max}) was comparable among all the groups. [*see Use in Specific Populations (8.6)*]

Pediatric: There are no pharmacokinetic data in pediatric patients.

Cytochrome P450: Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC_{50} values of > 30μM (> 11.5μg/mL). Bortezomib may inhibit 2C19 activity (IC_{50} = 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.

Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the in vitro chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the in vitro mutagenicity assay (Ames test) and in vivo micronucleus assay in mice.

Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat toxicity study, degenerative effects in the ovary were observed at doses ≥ 0.3 mg/m^2 (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2. VELCADE could have a potential effect on either male or female fertility.

13.2 Animal Toxicology and/or Pharmacology

Cardiovascular Toxicity: Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses ≥ 1.2 mg/m^2 induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Chronic Administration: In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for 2 weeks followed by 1-week rest), toxicities observed included severe anemia and thrombocytopenia, and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

14 CLINICAL STUDIES

14.1 Multiple Myeloma

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma:
A prospective, international, randomized (1:1), open-label clinical study of 682 patients was conducted to determine whether VELCADE administered intravenously (1.3 mg/m^2) in combination with melphalan

(9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Antiviral prophylaxis was recommended for patients on the VELCADE study arm.

The median age of the patients in the study was 71 years (48;91), 50% were male, 88% were Caucasian and the median Karnofsky performance status score for the patients was 80 (60;100). Patients had IgG/IgA/Light chain myeloma in 63%/25%/8% instances, a median hemoglobin of 105 g/L (64;165), and a median platelet count of 221,500 /microliter (33,000;587,000).

Efficacy results for the trial are presented in Table 11. At a pre-specified interim analysis (with median follow-up of 16.3 months), the combination of VELCADE, melphalan and prednisone therapy resulted in significantly superior results for time to progression, progression-free survival, overall survival and response rate. Further enrollment was halted, and patients receiving melphalan and prednisone were offered VELCADE in addition. A later, pre-specified analysis of overall survival (with median follow-up of 36.7 months with a hazard ratio of 0.65, 95% CI: 0.51, 0.84) resulted in a statistically significant survival benefit for the VELCADE, melphalan and prednisone treatment arm despite subsequent therapies including VELCADE based regimens. In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for the VELCADE, melphalan and prednisone treatment arm was 56.4 months and for the melphalan and prednisone treatment arm was 43.1 months, with a hazard ratio of 0.695 (95% CI: 0.57, 0.85).

Table 11: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study

Efficacy Endpoint	VELCADE, Melphalan and Prednisone n=344	Melphalan and Prednisone n=338
Time to Progression		
Events n (%)	101 (29)	152 (45)
Median[a] (months)	20.7	15.0
(95% CI)	(17.6, 24.7)	(14.1, 17.9)
Hazard ratio[b]	0.54	
(95% CI)	(0.42, 0.70)	
p-value[c]	0.000002	
Progression-free Survival		
Events n (%)	135 (39)	190 (56)
Median[a] (months)	18.3	14.0
(95% CI)	(16.6, 21.7)	(11.1, 15.0)
Hazard ratio[b]	0.61	
(95% CI)	(0.49, 0.76)	
p-value[c]	0.00001	
Response Rate		
CR[d] n (%)	102 (30)	12 (4)
PR[d] n (%)	136 (40)	103 (30)
nCR n (%)	5 (1)	0
CR + PR[d] n (%)	238 (69)	115 (34)
p-value[e]	$<10^{-10}$	
Overall Survival at median follow up of 36.7 months		
Events (deaths) n (%)	109 (32)	148 (44)
Median[a] (months)	Not Reached	43.1
(95% CI)	(46.2, NR)	(34.8, NR)
Hazard ratio[b]	0.65	
(95% CI)	(0.51, 0.84)	
p-value[c]	0.00084	

Note: All results are based on the analysis performed at a median follow-up duration of 16.3 months except for the overall survival analysis.

[a] Kaplan-Meier estimate

[b] Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: beta2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VELCADE, melphalan and prednisone

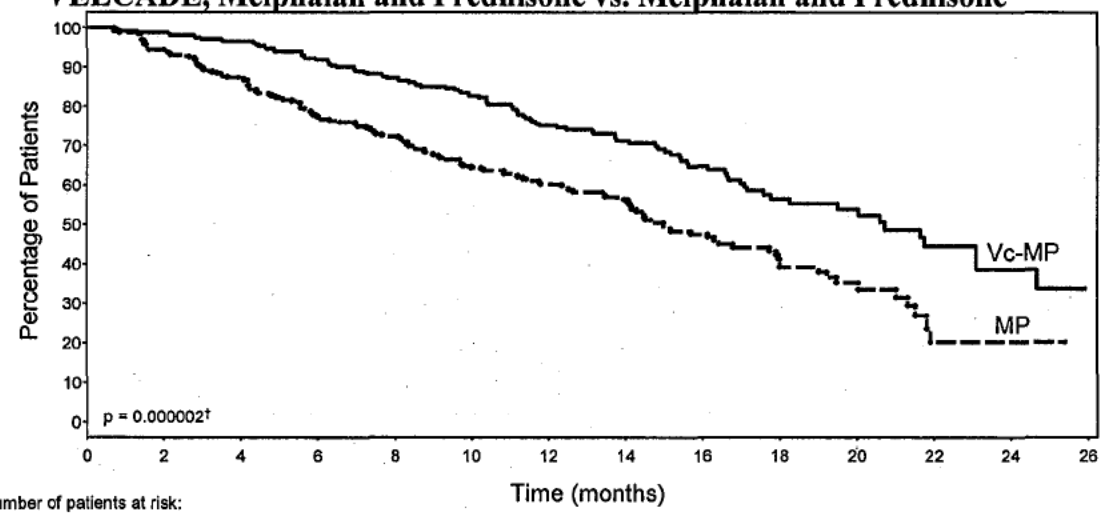
[c] p-value based on the stratified log-rank test adjusted for stratification factors: beta2-microglobulin, albumin, and region

[d] EBMT criteria

[e] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

TTP was statistically significantly longer on the VELCADE, melphalan and prednisone arm (see Figure 1). (median follow-up 16.3 months)

Figure 1: Time to Progression
VELCADE, Melphalan and Prednisone vs. Melphalan and Prednisone



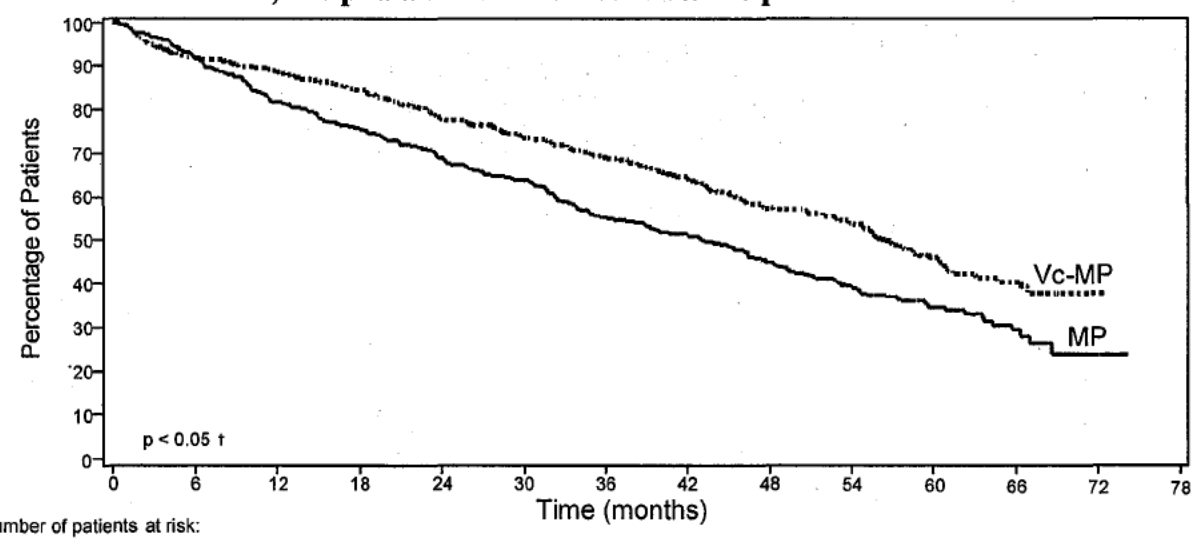
Number of patients at risk:

Vc-MP (n*)	344	309	280	258	240	200	159	114	81	53	35	20	13
MP (n*)	338	298	264	218	200	160	128	90	61	41	20	6	3

* Patients remaining after the indicated timepoint
† p-value from log-rank test

Overall survival was statistically significantly longer on the VELCADE, melphalan and prednisone arm (see Figure 2). (median follow-up 60.1 months)

Figure 2: Overall Survival
VELCADE, Melphalan and Prednisone vs. Melphalan and Prednisone



Number of patients at risk:

Vc-MP (n*):	344	300	288	270	246	232	216	199	176	158	78	34	1	0
MP (n*):	338	301	262	240	216	196	168	153	133	112	61	24	3	0

* Patients remaining after the indicated timepoint
† p-value from log-rank test

Randomized, Clinical Study in Relapsed Multiple Myeloma of VELCADE vs. Dexamethasone

A prospective phase 3, international, randomized (1:1), stratified, open-label clinical study enrolling 669 patients was designed to determine whether VELCADE resulted in improvement in time to progression (TTP) compared to high-dose dexamethasone in patients with progressive multiple myeloma following 1 to 3 prior therapies. Patients considered to be refractory to prior high-dose dexamethasone were excluded as were those with baseline Grade ≥ 2 peripheral neuropathy or platelet counts $< 50{,}000/\mu L$. A total of 627 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had previously received (1 previous line versus more than 1 line of therapy), time of progression relative to prior treatment (progression during or within 6 months of stopping their most recent therapy versus relapse > 6 months after receiving their most recent therapy), and screening β_2-microglobulin levels (≤ 2.5 mg/L versus > 2.5 mg/L).

Baseline patient and disease characteristics are summarized in Table 12.

Table 12: Summary of Baseline Patient and Disease Characteristics in the Relapsed Multiple Myeloma Study

Patient Characteristics	**VELCADE N=333**	**Dexamethasone N=336**
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: Male/female	56% / 44%	60% / 40%
Race: Caucasian/black/other	90% / 6% / 4%	88% / 7% / 5%
Karnofsky performance status score ≤70	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10^9/L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60% / 23% / 12%	59% / 24% / 13%
Median β_2-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤30 mL/min [n (%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%
Previous Therapy		
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

Patients in the VELCADE treatment group were to receive eight 3-week treatment cycles followed by three 5-week treatment cycles of VELCADE. Patients achieving a CR were treated for 4 cycles beyond first evidence of CR. Within each 3-week treatment cycle, VELCADE 1.3 mg/m^2/dose alone was administered by intravenous bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21).

Within each 5-week treatment cycle, VELCADE 1.3 mg/m^2/dose alone was administered by intravenous bolus once weekly for 4 weeks on Days 1, 8, 15, and 22 followed by a 13-day rest period (Days 23 to 35). [*see Dosage and Administration (2.1)*]

Patients in the dexamethasone treatment group were to receive four 5-week treatment cycles followed by five 4-week treatment cycles. Within each 5-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a 15-day rest period (Days 21-35). Within each 4-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered VELCADE at a standard dose and schedule on a companion study. Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients randomized to dexamethasone were offered VELCADE, regardless of disease status.

In the VELCADE arm, 34% of patients received at least one VELCADE dose in all 8 of the 3-week cycles of therapy, and 13% received at least one dose in all 11 cycles. The average number of VELCADE doses during the study was 22, with a range of 1 to 44. In the dexamethasone arm, 40% of patients received at least one dose in all 4 of the 5-week treatment cycles of therapy, and 6% received at least one dose in all 9 cycles.

The time to event analyses and response rates from the relapsed multiple myeloma study are presented in Table 13. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Complete response (CR) required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF$^-$). Partial response (PR) requires ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis; however, M-protein was still detectable by immunofixation (IF$^+$).

Table 13: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study

	All Patients		1 Prior Line of Therapy		> 1 Prior Line of Therapy	
	VELCADE	Dex	VELCADE	Dex	VELCADE	Dex
Efficacy Endpoint	**n=333**	**n=336**	**n=132**	**n=119**	**n=200**	**n=217**
Time to Progression						
Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median [a] (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio [b] (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value [c]	<0.0001		0.0019		<0.0001	
Overall Survival						
Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio [b] (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value [c,d]	<0.05		<0.05		<0.05	
Response Rate						
Population [e] n = 627	n=315	n=312	n=128	n=110	n=187	n=202
CR [f] n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR [f] n(%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR [f,g] n(%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR [f] n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value [h]	<0.0001		0.0035		<0.0001	

[a] Kaplan-Meier estimate

[b] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for VELCADE

[c] p-value based on the stratified log-rank test including randomization stratification factors

[d] Precise p-value cannot be rendered

[e] Response population includes patients who had measurable disease at baseline and received at least 1 dose of study drug

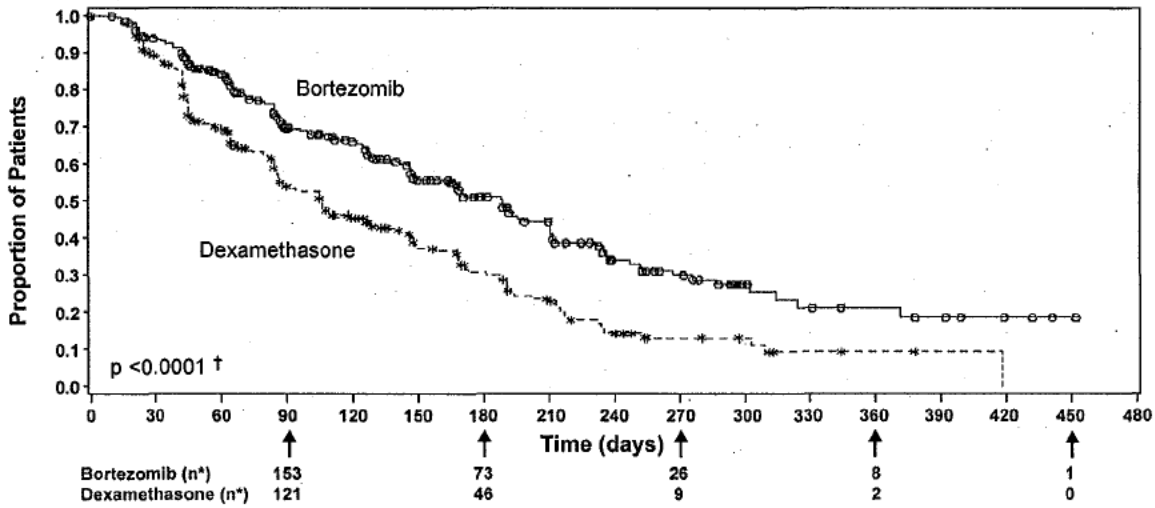
[f] EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria nCR is in the PR category

[g] In 2 patients, the IF was unknown

[h] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

TTP was statistically significantly longer on the VELCADE arm (see Figure 3).

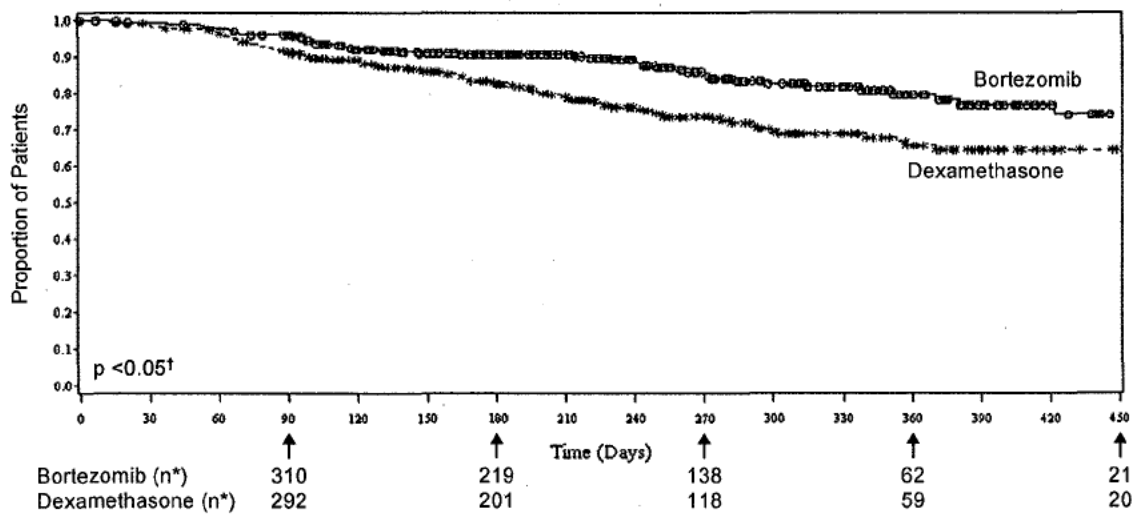
Figure 3: Time to Progression
Bortezomib vs. Dexamethasone (relapsed multiple myeloma study)



* Patients remaining after the indicated timepoint
† p-value from log-rank test

As shown in Figure 4 VELCADE had a significant survival advantage relative to dexamethasone ($p < 0.05$). The median follow-up was 8.3 months.

Figure 4: Overall Survival
Bortezomib vs. Dexamethasone (relapsed multiple myeloma study)



* Patients remaining after the indicated timepoint
† p-value from log-rank test

For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the dexamethasone arm. The response rate was significantly higher on the VELCADE arm regardless of β_2-microglobulin levels at baseline.

Randomized, Open-Label Clinical Study of VELCADE Subcutaneous vs. Intravenous in Relapsed Multiple Myeloma

An open-label, randomized, phase 3 non-inferiority study compared the efficacy and safety of the subcutaneous administration of VELCADE versus the intravenous administration. This study included 222 bortezomib naïve patients with relapsed multiple myeloma, who were randomized in a 2:1 ratio to receive 1.3 mg/m^2 of VELCADE by either the subcutaneous (n=148) or intravenous (n=74) route for 8 cycles. Patients who did not obtain an optimal response (less than Complete Response (CR)) to therapy with VELCADE alone after 4 cycles were allowed to receive oral dexamethasone 20 mg daily on the day of and after VELCADE administration (82 patients in subcutaneous treatment group and 39 patients in the intravenous treatment group). Patients with baseline Grade $\geq$ 2 peripheral neuropathy or neuropathic pain, or platelet counts < 50,000/μL were excluded. A total of 218 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had received (1 previous line versus more than 1 line of therapy), and international staging system (ISS) stage (incorporating beta$_2$-microglobulin and albumin levels; Stages I, II, or III).

The baseline demographic and others characteristics of the two treatment groups are summarized as follows: the median age of the patient population was approximately 64 years of age (range 38-88 years), primarily male (subcutaneous: 50%, intravenous: 64%); the primary type of myeloma is IgG (subcutaneous: 65% IgG, 26% IgA, 8% light chain; intravenous: 72% IgG, 19% IgA, 8% light chain), ISS staging I/II/III (%) was 27, 41, 32 for both subcutaneous and intravenous, Karnofsky performance status score was $\leq$ 70% in 22% of subcutaneous and 16% of intravenous, creatinine clearance was 67.5 mL/min in subcutaneous and 73 mL/min in intravenous, the median years from diagnosis was 2.68 and 2.93 in subcutaneous and intravenous respectively and the proportion of patients with more than one prior line of therapy was 38% in subcutaneous and 35% in intravenous.

This study met its primary (non-inferiority) objective that single agent subcutaneous VELCADE retains at least 60% of the overall response rate after 4 cycles relative to single agent intravenous VELCADE. The results are provided in Table 14.

Table 14: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs. Intravenous

	Subcutaneous VELCADE	Intravenous VELCADE
Intent to Treat Population	**n=148**	**n=74**
Primary Endpoint		
Response Rate at 4 cycles		
ORR (CR+PR) n(%)	63 (43)	31 (42)
Ratio of Response Rates (95% CI)	1.01 (0.73, 1.40)	
CR n (%)	11 (7)	6 (8)
PR n (%)	52 (35)	25 (34)
nCR n (%)	9 (6)	4 (5)
Secondary Endpoints		
Response Rate at 8 cycles		
ORR (CR+PR)	78 (53)	38 (51)
CR n (%)	17 (11)	9 (12)
PR n (%)	61 (41)	29 (39)
nCR n (%)	14 (9)	7 (9)
Median Time to Progression, months	10.4	9.4
Median Progression Free Survival, months	10.2	8.0
1-year Overall Survival (%)[a]	72.6	76.7

[a] Median duration of follow up is 11.8 months

A Randomized Phase 2 Dose-Response Study in Relapsed Multiple Myeloma

An open-label, multicenter study randomized 54 patients with multiple myeloma who had progressed or relapsed on or after front-line therapy to receive VELCADE 1 mg/m^2 or 1.3 mg/m^2 intravenous bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). The median duration of time between diagnosis of multiple myeloma and first dose of VELCADE on this trial was 2.0 years, and patients had received a median of 1 prior line of treatment (median of 3 prior therapies). A single complete response was seen at each dose. The overall response rates (CR + PR) were 30% (8/27) at 1 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

A Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma

Patients from the two phase 2 studies, who in the investigators' opinion would experience additional clinical benefit, continued to receive VELCADE beyond 8 cycles on an extension study. Sixty-three (63) patients from the phase 2 multiple myeloma studies were enrolled and received a median of 7 additional cycles of VELCADE therapy for a total median of 14 cycles (range 7 to 32). The overall median dosing intensity was the same in both the parent protocol and extension study. Sixty-seven percent (67%) of patients initiated the extension study at the same or higher dose intensity at which they completed the parent protocol, and 89% of patients maintained the standard 3-week dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed with prolonged VELCADE treatment. [*see Adverse Reactions (6.1)*]

14.2 Mantle Cell Lymphoma

A Phase 2 Single-arm Clinical Study in Relapsed Mantle Cell Lymphoma After Prior Therapy

The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicenter study of 155 patients with progressive disease who had received at least 1 prior therapy. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were Caucasian.

Of the total, 75% had one or more extra-nodal sites of disease, and 77% were stage 4. In 91% of the patients, prior therapy included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty seven percent (37%) of patients were refractory to their last prior therapy. An intravenous bolus injection of VELCADE 1.3 mg/m^2/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. Patients achieving a CR or CRu were treated for 4 cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity. [*see Dosage and Administration (2.4, 2.5)*]

Responses to VELCADE are shown in Table 15. Response rates to VELCADE were determined according to the International Workshop Response Criteria (IWRC) based on independent radiologic review of CT scans. The median number of cycles administered across all patients was 4; in responding patients the median number of cycles was 8. The median time to response was 40 days (range 31 to 204 days). The median duration of follow-up was more than 13 months.

Table 15: Response Outcomes in a Phase 2 Mantle Cell Lymphoma Study

Response Analyses (N = 155)	**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu + PR)	48 (31)	(24, 39)
Complete Response (CR + CRu)	12 (8)	(4, 13)
CR	10 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (23)	(17, 31)
Duration of Response	**Median**	**95% CI**
CR + CRu + PR (N = 48)	9.3 months	(5.4, 13.8)
CR + CRu (N = 12)	15.4 months	(13.4, 15.4)
PR (N=36)	6.1 months	(4.2, 9.3)

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

VELCADE® (bortezomib) for Injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

NDC 63020-049-01
3.5 mg single use vial

Unopened vials may be stored at controlled room temperature 25°C (77°F); excursions permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.

Consider handling and disposal of VELCADE according to guidelines issued for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact[1-4].

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following with patients prior to treatment with VELCADE:

Ability to Drive or Operate Machinery or Impairment of Mental Ability: VELCADE may cause fatigue, dizziness, syncope, orthostatic/postural hypotension. Advise patients not to drive or operate machinery if they experience any of these symptoms.

Dehydration/Hypotension: Patients receiving VELCADE therapy may experience vomiting and/or diarrhea. Advise patients how to avoid dehydration. Instruct patients to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

Pregnancy/Nursing: Advise patients to use effective contraceptive measures to prevent pregnancy during treatment with VELCADE. Instruct patients to report pregnancy to their physicians immediately. Advise patients that they should not receive VELCADE while pregnant or breast-feeding. If a patient wishes to restart breastfeeding after treatment, she should be advised to discuss the appropriate timing with her physician.

Concomitant Medications: Advise patients to speak with their physicians about any other medication they are currently taking.

Diabetic Patients: Advise patients to check their blood sugar frequently if using an oral antidiabetic medication and to notify their physicians of any changes in blood sugar level.

Peripheral Neuropathy: Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs.

Other: Instruct patients to contact their physicians if they develop a rash, experience shortness of breath, cough, or swelling of the feet, ankles, or legs, convulsion, persistent headache, reduced eyesight, an increase in blood pressure or blurred vision.

Distributed and Marketed by:
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

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U.S. Patents: 5,780,454; 6,083,903; 6,297,217 B1; 6,617,317 B1; 6,713, 446 B2; 6,958,319 B2; 7,119,080 B2; 6,747,150 B2

Rev 13

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director (Acting) Summary Review
NDA/BLA # **Supplement #**	21602 S-027
Applicant Name	Millenium Pharmaceuticals, Inc.
Date of Submission	March 23, 2011
PDUFA Goal Date	January 23, 2011
Proprietary Name / **Established (USAN) Name**	VELCADE® Bortezomib
Dosage Forms / Strength	3.5 mg vials
Proposed Indications	
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Firoozeh Alvandi, M.D., Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Statistical Review	Qing Xu, Ph.D., Mark D. Rothmann, Ph.D., Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	Wei Chen, Ph.D., Halh Saber, Ph.D.
CMC Review/OBP Review	Zedong Dong, Ph.D., Janice Brown, Ph.D.
Microbiology Review	Jessica Cole, Ph.D.
Clinical Pharmacology Review	Young-Jin Moon, Ph.D., Julie M. Bullock, Ph.D.
OPDP	Nisha Patel, Karen Rulli, Adora E. Ndu
CDTL Review	Julie M. Bullock, Ph.D.
OSE/DMEPA	Terri Wood-Cummings, M.D., Zachary Oleszczuk, Pharm.D., Carol Holquist, RPh
IRT/QT	Hao Zhu, M.D., Ph.D., Jeffry Florian, M.D., Ph.D., Monica L. Fiszman, M.D., Ph.D., Norman L. Stockbridge, M.D., Ph.D.

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epemiology
CDTL=Cross-Discipline Team Leader
IRT/QT=Interdisciplinary Review Team for QT Studies

Signatory Authority Review Template

1. Introduction

Millenium Pharmaceuticals, Inc. submitted this efficacy supplement (S-027) to support a new subcutaneous (SC) route of administration for VELCADE. The application is supported by the results of study MMY-3021, which was a randomized phase 3 study that compared the safety and efficacy of VELCADE administered by either the IV (as approved) or SC route in subjects with relapsed multiple myeloma. In addition, the sponsor submitted the results of a pilot phase 1 study of VELCADE administered by the IV and the SC routes (CAN-1004).

2. Background

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. VELCADE is approved by the FDA for the treatment of multiple myeloma and for the treatment of mantle cell lymphoma in patients who have received at least one prior therapy. VELCADE is adminstered as a bolus IV injection. The recommended dose is 1.3 mg/m^3 administered IV twice weekly for 2 weeks followed by a 10-day rest period. The drug product and the dosage for the SC route of administration will remain the same. However, the the drug will be more concentrated for SC administration (2.5 mg/mL) than for IV administration (1.0 mg/mL).

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the release and stability specifications, which are applicable in their current form for release for use both as IV and SC dosing. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. No changes to the non-clinical sections of the label are proposed.

5. Clinical Pharmacology/Biopharmaceutics

The Phase 3, randomized trial (MMY-3021) of 222 subjects with relapsed/refractory multiple myeloma included a substudy of 31 subjects to investigate the pharmacokinetics and pharmacodynamics of IV and SC VELCADE administration. In addition, a pilot Phase 1 study

of VELCADE administered by the IV and SC routes CAN-1004 was conducted. The study enrolled 24 subjects with multiple myeloma. There was comparable exposure with SC and IV routes of administration of bortezomib. The results of both studies indicated that the PK and PD of bortezomib are comparable, with the exception of lower C_{max} observed for SC dosing as compared to the IV administration. I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that would preclude approval, and that the results of the submitted trials are adequate to support approval of the SC route of administration.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

The Phase 3, randomized trial (MMY-3021) successfully demonstrated that the SC route of administration of VELCADE was non-inferior to the IV route of administration. A total of 222 subjects with relapsed/refractory multiple myeloma were enrolled and randomized 2:1 to SC and IV treatment groups. The demographics and baseline characteristics were similar and well-balanced between the treatment arms. The primary efficacy endpoint was the overall response rate (ORR) after 4 cycles of VELCADE. Non-inferiority was defined as retention of 60% of the IV treatment effect, as meased by ORR. The SC response rate was 43% and the IV response rate was 42% in the ITT population. I agree with the conclusions reached by the clinical and statistical reviewers. There are no outstanding clinical efficacy issues that would preclude approval.

8. Safety

The safety profile was comparable for the proposed new SC and the approved IV routes of administration. Patients treated with VELCADE SC as compared to patients treated with VELCADE IV had lower incidences of adverse events (95% vs. 99%), of grade ≥3 adverse events (57% vs. 70%), of peripheral sensory neuropathy (35% vs. 48%), of fatigue (12% vs. 22%), of adverse events leading to drug discontinuation (22% vs. 27%), and of adverse events leading to dose reduction (33% vs. 45%), dose withholding (30% vs. 39%), and dose delay (20% vs. 34%). I agree with the conclusions reached by the clinical reviewers. There are no outstanding safety issues that would preclude approval.

9. Advisory Committee Meeting

An Advisory Committee was not needed for this NDA supplement.

10. Pediatrics

N/A.

11. Other Relevant Regulatory Issues

Office of Medication Error Prevention and Risk Management provided recommendations on package insert labeling and carton and plastic tray lid labeling. These recommendations were accepted by the sponsor and implemented.
Office of Prescription Product Promotion provided comments on package insert labeling, which were reviewed by the review team and the sponsor and implemented as suggested.
The Interdisciplinary Review Team for QT Studies reviewed the QTc interval data provided by the sponsor in the Phase 1 study. No large changes in the mean QTc interval were detected. No significant concentration-ΔQTcF relationship was observed. Small increases in mean QTc interval (<10 ms) cannot be ruled out because of study design limitations.
There are no other unresolved relevant regulatory issues.

12. Labeling

OSE/DMEPA recommendations were implemented.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I concur with the assessments made by the review teams and recommend that the subcutaneous route of administration be approved.

- Risk Benefit Assessment

The subcutaneous route of administration has a favorable risk/benefit profile. The subcutaneous route of administration was found to be non-inferior to the approved IV route with respect to efficacy. Analysis of the safety results showed that patients treated with VELCADE administered subcutaneously as compared to patients treated with VELCADE administered intravenously had lower incidences of adverse events, of grade ≥3 adverse events, of peripheral sensory neuropathy, of fatigue, of adverse events leading to drug discontinuation, and of dose modification. The non-inferiority efficacy results, a possibly superior safety profile, and a less invasive route of administration provide adequate support for a positive benefit-to-risk assessment for subcutaneous VELCADE.

- Recommendation for Postmarketing Risk Management Activities

N/A.

- Recommendation for other Postmarketing Study Commitments

N/A.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDVARDAS KAMINSKAS
01/22/2012

Clinical Team Leader Review

Date	December 9, 2011
From	Virginia Kwitkowski, MS, RN, ACNP-BC
Subject	Clinical Team Leader Review
NDA/BLA # **Supplement#**	21602 Velcade (bortezomib) for Injection S-027
Applicant	Millennium Pharmaceuticals, Inc.
Date of Submission	March 23, 2011
PDUFA Goal Date	January 23, 2011
Proprietary Name / Established (USAN) names	**VELCADE® (bortezomib) for Injection**
Dosage forms / Strength	Solution; lyophilized powder for injection; single-use vial contains 3.5 mg of bortezomib
Proposed Indication(s)	1. Treatment of multiple myeloma 2. Treatment of mantle cell lymphoma in patients who have received at least 1 prior therapy
Recommended:	Approval

Millennium has submitted an efficacy supplement (S-027) to their NDA 21602 for Velcade for Injection. Millennium is requesting approval for the new subcutaneous route of administration for the existing approved indications of multiple myeloma and second line mantle cell lymphoma. The proposed dose is the same for subcutaneous and the approved intravenous route.

The supplement contains the results of a phase 3, randomized trial (MMY-3021) and a Phase I randomized pharmacokinetic/pharmacodynamic trial of subcutaneous and intravenous Velcade.

Recommended Regulatory Action: Approval of S-027.

Phase 3 Trial

The Phase 3, randomized trial (MMY-3021) successfully demonstrated that the subcutaneous route of administration for Velcade was non-inferior to the intravenous route of administration. In this trial, patients with relapsed multiple myeloma were randomized in a 2:1 fashion to receive subcutaneous or intravenous Velcade. Eligible patients were to have received at least one prior therapy for their disease and could not have received prior Velcade therapy.

The primary efficacy endpoint of this trial was overall response rate (ORR) after 4 cycles of Velcade, with the intent to demonstrate non-inferiority of SC compared to IV bortezomib for the primary endpoint, with non-inferiority defined as retention of 60% of the IV (active)

treatment effect (as measured by ORR). The trial design and non-inferiority margin were previously discussed with the Agency.

The FDA used the intent to treat population (ITT) of 148 subjects in the SC and 74 subjects in the IV arm for the efficacy analyses. The applicant used the response evaluable population data for efficacy analysis. Per the applicant's analysis, SC response rate for the primary endpoint of ORR after the first 4 cycles was 42% and IV response rate was 42%; using the ITT population, the SC response rate was 43% and the IV response rate was 42%. The subject who did not receive a dose of Velcade (randomized to SC group but did not receive any Velcade as the subject's condition deteriorated prior to study initiation) was removed from the ITT. This did not significantly impact the results as evident from the analysis using intent to treat versus response evaluable population. The secondary endpoints, though not statistically significant, supported the primary endpoint of non-inferiority for efficacy.

In the Phase 3 trial, the safety profile was comparable for the proposed new SC and previously approved IV routes of administration with 95% of subjects in the SC arm and 99% of subjects in the IV arm reporting at least 1 treatment-emergent AE. The SC treatment group had a lower incidence of: grade ≥3 adverse events (SC 57% versus IV 70%); adverse events leading to discontinuation (SC 22% versus IV 27%); adverse events leading to dose modification (dose reduction [SC 33% versus IV 45%]; dose withholding [SC 30% versus IV 39%]; and dose delay [SC 20% vs. IV 34%]). FDA analysis was consistent with that of the applicant.

The most common adverse events included anemia, neutropenia, thrombocytopenia, neuralgia, diarrhea, nauseas, vomiting, herpes zoster, and asthenia. Peripheral sensory neuropathy, all grades, was lower (35%) in the SC compared to IV (49%) treatment group as was grade ≥3 peripheral neuropathy (5% in the SC group compared to 15% in the IV group). Peripheral motor neuropathy all grades was similar in the two groups (5% in the SC and 4% in the IV group), while grade ≥3 peripheral motor neuropathy was lower in the SC group (0.68%) compared to the IV group (2.7%).

Summary of Phase 3 Trial: Velcade dosed at 1.3 mg/m^2 and injected subcutaneously on Days 1, 4, 8, and 11 of 21 day cycles is not inferior to the same dose and schedule of IV bolus Velcade. The safety profile may be improved by the subcutaneous route of administration as demonstrated by reduced incidence of severe adverse reactions and all grade peripheral sensory neuropathy in the patients randomized to the subcutaneous arm. The new route of administration also increases the convenience of receiving this treatment and avoids the risks associated with intravenous access.

Pharmacokinetic/Pharmacodynamic Trial

The randomized Phase 1 Trial (26866138-CAN-1004) had a primary objective to characterize the pharmacokinetics of the two routes of administration in patients with multiple myeloma after at least one prior line of therapy. The trial enrolled 24 patients (12 in each arm). The results indicated that from the 20 patients evaluable for PK and PD analysis, there was comparable exposure with SC and IV routes of administration of bortezomib. Plasma AUCs were similar after both single dose and repeat dose administration in both groups as were PD parameters (T_{max}, E_{max}, and AUE) as calculated by percent inhibition of 20S proteosome

activity-time data (change in proteosome activity from baseline). The mean maximum proteosome inhibition (E_{max}) and AUE_{0-27}) were comparable following IV and SC administration of bortezomib. C_{max} after SC administration was lower than after IV administration.

Summary of PK/PD Trial: The exposure to Velcade was similar between the subcutaneous and intravenous arms.

Usability Testing

DMEPA identified concerns about the results of a usability testing study submitted by Millennium that demonstrated a 31% error rate during testing of health care providers during preparation of Velcade for administration (for both routes of administration). In response to these concerns, the Division of Hematology Products has sent an Information Request to Millennium requesting that they provide a plan for addressing these errors:

"Given the results of the usability testing study submitted with S-027, conducted by (b) (4) *demonstrating that 14 out of 45 participants (31%) committed at least one error during preparation of Velcade for administration, we are requesting that you propose your plans to enhance the accuracy of Velcade reconstitution and preparation in the community."*

The Division does not typically request usability testing for parenteral oncology products, and should not be an approvability issue for this supplement.

Labeling negotiations are ongoing at the time of this review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIRGINIA E KWITKOWSKI
12/09/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

CROSS DISCIPLINE TEAM LEADER REVIEW

CROSS-DISCIPLINE TEAM LEADER REVIEW

Date	January 8, 2012
From	Julie M. Bullock, Pharm.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	21-602 S-027/SDN278
Applicant	Millennium Pharmaceuticals, Inc.
Date of Submission	23 March 2011
PDUFA Goal Date	23 January 2012
Proprietary Name / Established (USAN) names	VELCADE® (bortezomib)
Dosage forms / Strength	3.5 mg vials
Proposed Indication(s)	No new indications proposed, new route (subcutaneous)
Recommended Action:	Approval

1. INTRODUCTION

This review summarizes the multi-disciplinary evaluation of the information submitted by Millennium Pharmaceuticals to support a new subcutaneous (SC) route of administration for VELCADE. The Applicant submitted the results of study MMY-3021 which was a randomized, phase 3 study that compared the safety and efficacy of VELCADE administered by either IV or SC route in subjects with progressive disease after prior systemic therapy for multiple myeloma. In addition, a pilot phase 1 study of VELCADE administered by the IV and SC routes (CAN-1004) was conducted.

Study MMY-3021 met the non-inferiority objective for the primary efficacy endpoint of overall response rate (complete response + partial response) after 4 cycles of VELCADE in patients treated with subcutaneous VELCADE compared with the currently approved intravenous route of administration. The patients randomized to the subcutaneous route achieved a response rate of 43% compared with 42% in those randomized to the intravenous treatment group. The non-inferiority margin was 0.6 (95% CI 7.0-27.9) [p=.00106].

With regard to certain adverse reactions associated with VELCADE (peripheral neuropathy), the subcutaneous route of administration had a more favorable safety profile. The subcutaneous route of administration also offers the added convenience of lack of need for intravenous access and avoidance of the complications associated with intravenous access.

In conclusion, the recommended regulatory action is approval of the new subcutaneous route of administration of VELCADE for the treatment of multiple myeloma.

2. BACKGROUND

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. VELCADE is currently approved in the US for the treatment of multiple myeloma and is also indicated for the treatment of mantle cell lymphoma in patients who have received at least 1 prior therapy. VELCADE is licensed for administration as a bolus intravenous (IV) injection through a peripheral or central IV line. The recommended dosage in relapsed multiple myeloma and mantle cell lymphoma is 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous (IV) injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). The recommended dosage in previously untreated multiple myeloma is 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous (IV) injection in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles. In Cycles 1-4, VELCADE is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, VELCADE is administered once weekly (Days 1, 8, 22 and 29).

Based on the efficacy and safety results of study MMY-3021 and PK findings of study CAN-1004 the Applicant is proposing changes in the Highlights, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, and Clinical Studies of the label.

3. CMC/DEVICE

The applicant states that all aspects of manufacturing and release of the drug product vials remain unchanged from the currently approved intravenous dose. The release and stability specifications were assessed by the Chemistry Reviewer Dr. Zedong Dong, and are applicable in their current form for release for use both as IV and SC dosing.

The currently approved IV dose schedule allows for reconstitution of the drug product lyophilized cake with 3.5 mL 0.9% Sodium Chloride for Injection for a final concentration of 1.0 mg/mL. The proposed SC dose schedule allows for reconstitution of the drug product lyophilized cake with 1.4 mL for a final concentration of 2.5 mg/mL.

Dr. Dong's review focused on the in-use stability of the reconstituted solution and its compatibility with various syringes. Three types of commercial syringes from different vendors were tested during the compatibility study, with the reconstituted drug product (2.5 mg/mL, Lot ZC070A) in the syringes being held for up to (b) (4) at room temperature in ambient light. Based on the results, the reconstituted drug product solution (2.5 mg/mL) for subcutaneous injection appears to be compatible with the commercial syringes tested.

In-use stability studies of the 2.5 mg/mL reconstituted solution were conducted in both syringes and vials to support the proposed maximum storage duration of 8 hours under room temperature and ambient light as outlined in the labeling in Section 2.8. According to Dr. Dong, there were no other proposed CMC related changes in the package insert and no CMC related changes were made to the carton and immediate container labeling.

The applicant requested for categorical exclusion from environmental assessment as per 21CFR 25.31(b). And according to Dr. Dong, the request may be granted.

Dr. Jessica Cole from Product Quality Microbiology reviewed the supplement with an NAI on 11/10/2011.

The Applicant submitted the results of a Human Factors study conducted to evaluate whether VELCADE would be reconstituted correctly and that users would draw up the correct dose for delivery to patients via the prescribed route (intravenous or subcutaneous). VELCADE will be reconstituted by hospital pharmacy personnel, including pharmacists and pharmacy technicians. It will also be reconstituted by registered nurses who work on oncology units or in private clinics. The results of the study show that fourteen (31.1%) out of the 45 participants committed a total of one or more use errors when performing the hands-on tasks. I agree with the Medical Officer's conclusion that the results of this usability study do not indicate that the errors were due to flaws in the package design. In order to enhance the accuracy of drug reconstitution and administration, the Agency will request that the Applicant propose methods for communication of the proper methods of reconstitution and preparation of the VELCADE for each route of administration to the health care community. Human Factor and Usability testing is not required for other parenteral oncology products presently marketed. VELCADE will not be reconstituted or administered by patients or caregivers.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Results of two repeat-dose studies in monkey and a local tolerance study in rabbit were submitted to support the change in the route of administration. The 4-cycle subcutaneous and intravenous injection comparative toxicity/ PK study in cynomolgus monkey is considered as the pivotal study. Results of the monkey study indicate that toxicities are comparable for the SC and IV route of administration and that the PK is also comparable with the exception of lower Cmax observed for SC dosing in cycle 1 as

compared to the IV administration (as seen in blood or plasma). The significance of the difference in the exposure is unclear as this trend was not evident in other dosing cycles.

No changes to the non-clinical sections of the label are proposed.

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

The design of trials CAN-1004 and MMY-3021 are described in full detail in Dr. Firoozeh Alvandi and Dr. Young-Jin Moon's reviews. In short, MMY-3021 was a multi-center, randomized, non-inferiority study of VELCADE administered by either the IV or SC route in patients with multiple myeloma. The primary objective of the study was overall response rate (ORR) after 4 cycles. Trial CAN-1004 was a pilot randomized, multicenter, phase 1 study of VELCADE administered by the IV and SC routes in 24 subjects with multiple myeloma. This study characterized PK, PD, safety and efficacy of subcutaneous VELCADE and formed the basis of the design of the Phase 3 MMY-3021 study.

I concur with Dr. Moon's interpretation of the PK and PD findings and conclusions which are summarized below:

- At the 1.3 mg/m^2 dose, bortezomib PK parameters were comparable for the SC injected solution of 1 mg/mL (Study CAN-1004) and 2.5 mg/mL (Study MMY-3021).
- In both studies bortezomib maximum plasma concentration (Cmax) was lower for SC administration relative to IV bolus administration.
- Bortezomib total systemic exposure (AUC) following SC injection was comparable to that of the IV injection.
- The mean maximum % inhibition of 20S proteasome activity (Emax) and the area under the effect time curve for proteasome inhibition (AUE) were comparable between the SC and IV routes.

I agree with Dr. Moon's conclusion that the submitted trials are adequate to support approval of the SC route of administration.

6. CLINICAL MICROBIOLOGY

Not applicable.

7. CLINICAL/STATISTICAL- EFFICACY

A full description of the study design for MYY-3021 and patient demographics are provided by Dr. Firoozeh Alvandi in the Medical Officer review. The primary objective of study MYY-3021 was overall response rate (CR+PR) after 4 cycles.

A total of 222 subjects with relapsed/refractory multiple myeloma who had received 1-3 prior lines of therapy (but who had not received VELCADE previously) were enrolled and randomized 2:1 to SC and IV treatment groups (148 in the SC arm and 74 in the IV arm). The median age was 64.5 years in both arms. There were more males (64%) in the IV group than females.

I agree with Dr. Alvandi's conclusions that demographics, baseline characteristics, including disease characteristics and other clinical parameters, were similar and well-balanced between the treatment groups. When imbalanced, the baseline parameters tended to be less favorable for the SC group (greater number of subjects with worse disease characteristics in the SC group than the IV group), potentially negatively impacting efficacy and safety of the SC group compared to IV.

The intent to treat population (ITT) of 148 subjects in the SC and 74 subjects in the IV arm was used for efficacy analyses. The SC response rate was 43% and the IV response rate was 42%. The response rate of the IV route of administration (42%) was similar to the rate in the 2005 VELCADE approval for use in

multiple myeloma patients with at least one line of prior therapy (38%). For an analysis of secondary endpoints from study MYY-3021 please see Dr. Alvandi's Medical Officer review.

8. SAFETY

I agree with the assessments made by Dr. Alvandi with respect to the safety findings in MYY-3021. The safety profile was comparable for the proposed new SC and previously approved IV routes of administration with 95% of subjects in the SC arm and 99% of subjects in the IV arm reporting at least 1 treatment-emergent AE. The SC treatment group had a lower incidence of:

- grade ≥3 adverse events (SC 57% versus IV 70%);
- adverse events leading to discontinuation (SC 22% versus IV 27%);
- adverse events leading to dose modification (dose reduction [SC 33% versus IV 45%];
- dose withholding [SC 30% versus IV 39%];
- and dose delay [SC 20% vs. IV 34%]).

The most common adverse events included anemia, neutropenia, thrombocytopenia, neuralgia, diarrhea, nauseas, vomiting, herpes zoster, and asthenia. TABLE 2 below summarizes the safety analysis for adverse events occurring in ≥10% of subjects.

TABLE 1. AE in ≥10% of Subjects - Safety-Evaluable Population

Adverse Event	SC All Grades (%) n= 147	IV All Grades (%) n=74	SC Grade 3-4 (%)	IV Grade 3-4 (%)
ANAEMIA	56 (37.8)	26 (35.1)	19 (12.8)	6 (8.11)
THROMBOCYTOPENIA	53 (35.8)	27 (36.5)	21 (14. 2)	14 (18.9)
PERIPHERAL SENSORY NEUROPATHY	52 (35.1)	36 (48.6)	7 (4.73)	11 (14.9)
NEUTROPENIA	42 (28.4)	20 (27)	26 (17.6)	13 (17.6)
DIARRHOEA	36 (24.3)	27 (36.5)	3 (2.03)	4 (5.41)
NEURALGIA	35 (23.6)	17 (23)	5 (3.38)	7 (9.46)
LEUKOPENIA	29 (19.6)	16 (21.6)	9 (6.08)	5 (6.76)
NAUSEA	28 (18.9)	14 (18.9)	0 (0)	0 (0)
PYREXIA	28 (18.9)	14 (18.9)	0 (0)	0 (0)
ASTHENIA	24 (16.2)	14 (18.9	4 (2.7)	4 (5.41)
WEIGHT DECREASED	22 (14.9)	3 (4.05)	0 (0)	1 (1.35)
BACK PAIN	21 (14.2)	8 (10.8)	1 (0.68)	2 (2.7)
CONSTIPATION	21 (14.2)	11 (14.9)	1 (0.68)	1 (1.35)
FATIGUE	18 (12.2)	16 (21.6)	3 (2.03)	3 (4.05)
INSOMNIA	18 (12.2)	8 (10.8)	0 (0)	0 (0)
HERPES ZOSTER	17 (11.5)	7 (9.46)	3 (2.03)	1 (1.35
VOMITING	17 (11.5)	12 (16.2)	3 (2.03)	1 (1.35)

9. ADVISORY COMMITTEE MEETING

An advisory committee meeting was not needed for this supplement.

10. PEDIATRICS

Not applicable.

11. OTHER RELEVANT REGULATORY ISSUES

There are no relevant regulatory issues for Application Integrity Policy, nor are there any exclusivity or patent issues of concern for this supplement.

Dr. Alvandi reviewed the financial disclosures for study MYY-3021. The applicant stated that they were not able to obtain financial disclosures from 10 investigators who participated. The applicant provided documentation which indicated that diligent effort was made to obtain the disclosures, including a second written request for financial disclosure to the investigators when the first had not been returned. The applicant also stated that there will be a one-year post trial completion IFDF due in February 2012 at which time financial updates will be requested. I agree with Dr. Alvandi's conclusion that there was no evidence of financial arrangements that would be expected to impact data reliability.

Division of Scientific Investigations (DSI) audit was not considered necessary for this application because no single site enrolled a disproportionately large proportion of subjects. Also, the various sites enrolled relatively few subjects such that if the data obtained from one site were invalid, it would not be expected to affect the efficacy or safety results of the trial.

There are no outstanding Post Marketing Commitments.

12. LABELING

The applicant has proposed major changes to the product label in Highlights, Sections 2, 5, 11, 12 and 14. The sponsors proposed changes included relevant safety, efficacy and PK information from study MYY-3021 in addition to administration changes to add the subcutaneous route.

The applicant's proposed changes to the package insert (label) and medication guide have been reviewed by the clinical, clinical pharmacology, and statistical reviewers, as well as by the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Division of Medication Error Prevention and Analysis (DMEPA).

The review team has recommended changes to the sponsors proposed labeling in Sections 2, 5, 11 and 14. The sponsors additions to section 12 were found acceptable. The review team's revisions should be incorporated into the final label.

13. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

13.1. Recommended Regulatory Action

I concur with the assessments made by the review team and recommend that the subcutaneous route of administration be approved. The labeling revisions recommended by the review team should be incorporated into the final label.

13.2. Risk-Benefit Assessment

The subcutaneous route of administration has a favorable risk benefit profile. The subcutaneous route of administration was found to be non-inferior to the approved IV route with regard to efficacy. Analysis of efficacy results from the randomized trial comparing SC to IV route of administration (MMY-3021) met the primary objective of non-inferiority for the primary efficacy endpoint of ORR (CR+PR) after 4 cycles of VELCADE for both SC and IV routes. The ORR was 43% in SC and 42% in the IV treatment group using the Intent to Treat (ITT) population (with a 95% CI for the difference in ORR-SC-0.6 ORR_IV of 7.0, 27.9) [p= 0.001].

Analysis of the safety results of this pivotal trial found a lower incidence of all grade peripheral sensory neuropathy in patients who received VELCADE by the SC route of administration (35%) compared to those who received the IV route of administration (49%). Severe (grade 3 or higher) peripheral neuropathy was also less common in the SC group (5% vs. 15%). Peripheral motor neuropathy all grades was similar in the two groups (5% SC vs. 4% IV), while grade ≥3 peripheral motor neuropathy was lower in the SC group (0.7% vs. 2.7%).

The non-inferior efficacy results, a possibly improved safety profile, and a less invasive route of administration provide adequate support for a positive Benefit to Risk assessment for subcutaneous VELCADE.

13.3. Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable

13.4. Recommendation for other Postmarketing Requirements and Commitments

Not applicable

13.5. Recommended Comments to Applicant

Not applicable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE M BULLOCK
01/08/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21602 Supplement-027
Priority or Standard	Standard
Submit Date(s)	March 23, 2011
Received Date(s)	March 23, 2011
PDUFA Goal Date	January 23, 2012
Division / Office	Division of Hematology Products
Reviewer Name(s)	Firoozeh Alvandi, MD
Review Completion Date	December 09, 2011
Established Name	Bortezomib
(Proposed) Trade Name	Velcade for Injection
Therapeutic Class	Antineoplastic
Applicant	Millennium Pharmaceuticals, Inc.
Formulation(s)	Solution; lyophilized powder for injection
Dosing Regimen	Subcutaneous Injection 1.3mg/m^2/dose (twice weekly for two weeks of a three week cycle: days 1, 4, 8, 11)
Indication(s)	Treatment of multiple myeloma Treatment of mantle cell lymphoma in patients who have received at least 1 prior therapy
Intended Population(s)	Patients with multiple myeloma

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based upon my review of the data submitted in support of this efficacy supplement, the recommended regulatory action is approval of the new subcutaneous route of administration of Velcade for the treatment of multiple myeloma. This recommendation is based upon the results of a single, randomized open label phase 3 trial, MMY-3021. The trial has met the non-inferiority objective for the primary efficacy endpoint of overall response rate (complete response + partial response) after 4 cycles of Velcade in patients treated with subcutaneous Velcade compared with the currently approved intravenous route of administration. The patients randomized to the subcutaneous route achieved a response rate of 43% compared with 42% in those randomized to the intravenous treatment group. The non-inferiority margin was 0.6 (95% CI 7.0-27.9) [p=.00106].

The new, subcutaneous, route of administration of Velcade was comparable in efficacy. With regard to certain adverse reactions associated with Velcade (peripheral neuropathy), the subcutaneous route of administration had a more favorable safety profile. The subcutaneous route of administration also offers the added convenience of lack of need for intravenous access and avoidance of the complications associated with intravenous access.

In the trial, both subcutaneous and intravenous Velcade were administered in the office by health care providers. The proposed label reviewed does not provide for self-administration with subcutaneous (SC) Velcade.

1.2 Risk Benefit Assessment

The subcutaneous route of administration has a favorable risk benefit profile. The subcutaneous route of administration was found to be non-inferior to the approved IV route with regard to efficacy. Analysis of efficacy results from the randomized trial comparing SC to IV route of administration (MMY-3021) met the primary objective of non-inferiority for the primary efficacy endpoint of ORR (CR+PR) after 4 cycles of Velcade for both SC and IV routes. The ORR was 43% in SC and 42% in the IV treatment group using the Intent to Treat (ITT) population (with a 95% CI for the difference in ORR-SC-0.6 ORR_IV of 7.0, 27.9) [p= 0.001].

Analysis of the safety results of this pivotal trial found a lower incidence of all grade peripheral sensory neuropathy in patients who received Velcade by the SC route of administration (35%) compared to those who received the IV route of administration (49%). Severe (grade 3 or higher) peripheral neuropathy was also less common in the

SC group (5% vs. 15%). Peripheral motor neuropathy all grades was similar in the two groups (5% SC vs. 4% IV), while grade ≥3 peripheral motor neuropathy was lower in the SC group (0.7% vs. 2.7%).

The non-inferior efficacy results, a possibly improved safety profile, and a less invasive route of administration provide adequate support for a positive Benefit to Risk assessment for subcutaneous Velcade.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No new recommendations are indicated on the basis of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

No new recommendations are indicated on the basis of this review.

2 Introduction and Regulatory Background

2.1 Product Information

Velcade™ (bortezomib) for Injection is an antineoplastic agent that was initially approved in 2003 for the treatment of relapsed and refractory multiple myeloma. It is currently indicated as a single agent at the dose of 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous injection twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10-day rest period, every three weeks, in relapsed multiple myeloma and mantle cell lymphoma, previously treated with at least 1 therapy (see section 2.6 for additional details). Velcade for Injection is available by prescription in single use vial containing 3.5 mg bortezomib as sterile lyophilized powder with 35 mg mannitol as inactive ingredient.

With this supplemental NDA, the Applicant proposes a new subcutaneous route of administration.

Bortezomib is a modified dipeptidyl boronic acid. The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)- oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

2.2 Tables of Currently Available Treatments for Proposed Indications

Current available treatment options for multiple myeloma are listed in Table 1 below.

Table 1 Currently Available Treatment for Multiple Myeloma

Name of Drug	Line of Therapy
Bortezomib	1st line
Melphalan	1st line
Cyclophosphamide	1st line
Carmustine + Prednisone	1st line
Thalidomide + Dexamethasone	1st line
Lenalidomide + Dexamethasone	2nd line
Pegylated liposomal doxorubicin + bortezomib	2nd line

Current available treatment options for relapsed multiple myeloma include Velcade (bortezomib), Doxil (pegylated liposomal doxorubicin), or Revlimid (lenalidomide), dexamethasone, or combinations including these agents.

2.3 Availability of Proposed Active Ingredient in the United States

The drug and its proposed active ingredients are currently available and marketed in the United States. The product proposed for subcutaneous administration contains the same active ingredients and excipients as the currently marketed approved intravenous injection. A literature and web search, including query of the EMA website for authorized, refused, withdrawn, or suspended medicines revealed no prior submission for approval of the SC route of bortezomib.

Common adverse events associated with Velcade are asthenic conditions, diarrhea, nausea, constipation, peripheral neuropathy, vomiting, pyrexia, thrombocytopenia, psychiatric disorders, anorexia and decreased appetite, neutropenia, neuralgia, leucopenia, and anemia

2.4 Important Safety Issues With Consideration to Related Drugs

Velcade (bortezomib) is the only FDA approved proteosome inhibitor and it is indicated for the treatment of patients with multiple myeloma, and for treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On August 16, 2007, a Type B meeting was held, under IND 056515, between representatives of Millennium Pharmaceuticals, Inc. and the Division of Drug Oncology

Products of FDA to discuss the clinical development plan and clinical trial design intended to lead to the addition of a subcutaneous (SC) injection route to the dosage and administration section of the Velcade package insert. In this meeting, Millennium proposed using a non-inferiority margin retaining 60% of the effect on response rate. The proposed non-inferiority trial compared the subcutaneous route of administration to the approved intravenous route of administration. The Division requested that Millennium provide details regarding the response rate assumptions and calculations for the proportion retention approach, recommending that the applicant use lower 95% confidence bound of Velcade IV effect size as the estimate for active control effect. The Agency also stated that although the proposed single arm PK/PD trial would be sufficient to demonstrate that SC and IV administration provide similar Velcade exposure, it will not demonstrate bioequivalence.

On March 21, 2008, the applicant submitted protocol 26866138-MMY-3021, a phase 3, non-inferiority comparison of subcutaneous Velcade to intravenous Velcade, with 192 subjects with previously treated multiple myeloma for enrollment, randomized in a 2:1 ratio (subcutaneous : intravenous Velcade). In July 2008, following review and meeting with the applicant, the FDA advised the applicant to increase planned enrollment in the proposed protocol to 216 patients and to base the non-inferiority analysis of the primary endpoint (response rate) on the lower 95% confidence interval of prior IV Velcade experiences with 60% retention of effect (overall response rate of 35.5%). A 60% retention of effect was deemed acceptable by the Agency, given that the drug was the same.

2.6 Other Relevant Background Information

Velcade™ (bortezomib) for Injection was initially approved on May 13, 2003 for treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy (determination of effectiveness of Velcade was based on response rates). Subsequent trials demonstrated a survival advantage for Velcade compared to dexamethasone and the label was modified on March 25, 2005 to reflect this finding and to indicate use in a multiple myeloma patient population after receipt of at least 1 prior therapy.

On December 8, 2006, the new indication was added for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

On June 20, 2008 the label indication was modified to state that Velcade is indicated for: 1) treatment of patients with multiple myeloma and 2) treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

A search of the literature and query of the EMA did not find approval of SC Velcade in other countries/regions.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the eCTD submission was adequate and sufficient to allow substantive review. However, the submission did not contain raw data sets, which were requested subsequently in the "74 day letter" and on September 14, 2011. The applicant replied by e mail stating that the requested information can be found on CRT 046/m5/datasets/26866138-MMY-3021/analysis/datasets (e mail received from applicant on September 15, 2011).

3.2 Compliance with Good Clinical Practices

The applicant has provided the following statement of compliance with Good Clinical Practice: *"This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Known instances of nonconformance were documented and are not considered to have had an impact on the overall conclusions of this study."* The trial was conducted under IRB and informed consent was obtained form trial participants/patients prior to enrollment.

Subjects were consented prior to study participation.

Division of Scientific Investigations (DSI) audit was not considered important for this application because no single site enrolled a disproportionately large proportion of subjects. Also, the various sites enrolled relatively small number of subjects such that if the data obtained from one site were to be invalid, it would not be expected to affect the efficacy or safety results of the trial.

Protocol Violations
Of the 148 subjects enrolled in the SC and 74 subjects enrolled in the IV groups, 25 subjects (17%) in the SC group and 14 subjects (19%) in the IV group had protocol violations/deviations. Major protocol deviations are summarized in Figure 1 below.

Though deviations in baseline assessments were numerically higher in the SC group, the numbers were overall low, and not likely to affect the trial results.

Figure 1 Major Protocol Deviations MMY-3021

Protocol Deviation Coded Term	IV (N=74) n (%)	SC (N=148) n (%)	Total (N=222) n (%)
Total no. subjects with deviation	14 (19)	25 (17)	39 (18)
Baseline assessment deviation	1 (1)	4 (3)	5 (2)
Excluded concomitant medication	3 (4)	7 (5)	10 (5)
Selection criteria not met	5 (7)	6 (4)	11 (5)
Subject non-compliance	2 (3)	5 (3)	7 (3)
Treatment deviation	5 (7)	8 (5)	13 (6)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Source: Clinical Study Report, Section 4.4

3.3 Financial Disclosures

The applicant stated that they were not able to obtain financial disclosures from 10 investigators who participated in the trial and did not provide documentation or discussion of diligent efforts to obtain the disclosure. A request for this information was communicated to the applicant in the "74 day letter", on May 27, 2011. The applicant's response was received on October 20, 2011 and was found to be adequate. The applicant provided a document outlining the process by which financial disclosures are obtained, which indicated that diligent effort was made to obtain the disclosures, including a second written request for financial disclosure to the investigators when the first had not been returned. The applicant also stated that there will be a one-year post trial completion IFDF due in February 2012 at which time financial updates will be requested. From the material submitted and reviewed there was no evidence of financial arrangements that would be expected to impact data reliability.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC review recommends approval of the supplement from the CMC perspective, concluding that release and stability specifications of this marketed drug product are applicable to both IV and SC routes of administration; that the currently approved IV dose schedule allows for reconstitution of the drug product lyophilized cake with 3.5 mL 0.9% Sodium Chloride for Injection for a final concentration of 1.0mg/mL, and that the proposed SC dose schedule allows for reconstitution of the drug product lyophilized

cake with 1.4 mL for a final concentration of 2.5 mg/mL. The CMC review also found and concluded that the reconstituted drug product solution (2.5 mg/mL) for subcutaneous injection is compatible with three different commonly used commercial syringes tested and that the in-use stability of the reconstituted solution is acceptable. No CMC issues were identified that would preclude approval. On October 4, 2011, the applicant submitted an amendment to labeling, based on additional usibility study/test information, for review. As of the completion of this review, CMC has not finalized review of the amendment to labeling. The reader is referred to the CMC review for the final conclusion.

4.2 Clinical Microbiology

A Clinical Microbiology consult request was sent by CMC on October 18, 2011. See Section 4.1 CMC review, above for CMC conclusions. The results of the consult have not been finalized as of the completion of this clinical review. The reader should refer to the CDTL (cross disciplinary team leader) review by Julie Bullock, PhD, and to the CMC review by Zedong Dong, PhD.

4.3 Preclinical Pharmacology/Toxicology

Pharmacology/Toxicology review of two repeat-dose studies in monkeys (the pivotal 4-cycle subcutaneous and intravenous injection comparative toxicity/ PK study in cynomolgus monkeys was considered the pivotal study) and a local tolerance study in rabbits submitted in support of this supplemental NDA, found the toxicities for the SC and IV route of administration to be comparable and the PK to also be comparable with the exception of lower C_{max} observed for SC dosing in cycle 1 as compared to the IV administration (as seen in blood or plasma), although the significance of the difference in the exposure was unclear (as this trend was not evident in other dosing cycles). The Pharmacology/Toxicology review concluded that the nonclinical studies adequately support approval of the new route of administration proposed in the supplemental NDA, form the preclinical perspective. The review also concluded that no labeling changes to nonclinical sections would be necessary and that no additional nonclinical studies were deemed necessary at this time.

4.4 Clinical Pharmacology

Clinical Pharmacology review of the pivotal clinical study MMY-3021 and of the supporting PK study CAN-1004, concluded that PK and PD of bortezomib IV and SC are comparable, with the exception of lower C_{max} observed for SC dosing as compared to the IV administration and found the results of these studies adequately support approval of this supplemental NDA from the Clinical Pharmacology perspective. The review also found the methods (liquid chromatography coupled to tandem mass spectrometry) to obtain the data presented on plasma samples analyzed for

concentrations of bortezomib adequately validated, and the assay accuracy, precision, LLOQ and range/linearity acceptable. The applicant's proposed language for the Pharmacokinetics section of the label (Section 12.3), [redacted] was deemed acceptable from the Clinical Pharmacology perspective.

4.4.1 Mechanism of Action

Velcade is a ubiquitin-protease inhibitor. It is a reversible inhibitor of chymotrypsin-like activity of the 26S proteasome in mammalian cells. Its activity in multiple myeloma is thought to be through various mechanisms, including inhibition of nuclear factor κB (NF-κB) activation, attenuation of interleukin-6 (IL-6)-mediated cell growth, direct apoptotic effect, and possibly antiangiogenic effects.

4.4.2 Pharmacodynamics

In a randomized phase 1 trial performed in 24 patients with relapsed/refractory multiple myeloma who received IV or SC injections of Velcade 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 cycles, more than 90% of subjects exhibited greater than 50% proteasome inhibition for at least 1 or more time points for both treatments. Reversibility of 20S proteasome inhibition in whole blood was demonstrated in samples collected over 72 hours following drug administration. There was no significant difference in overall proteasome inhibition activity or in overall systemic exposure over the studied time period between the two routes of administration. This trial will be reviewed in more detail in section 5.3. No specific review of CYP inhibition was indicated, as this is a previously approved/marketed drug with known profile of the drug for IV administration which has comparable PK/PD profile for both the IV and new SC routes of administration.

QT Prolongation

Millenium submitted the study report for Protocol 26866138-CAN-1004 titled "Comparison of Pharmacokinetics and Pharmacodynamics of Subcutaneous Versus Intravenous Administration of Bortezomib in Patients With Multiple Myeloma" along with electronic datasets and ECG waveforms to the ECG warehouse. The QT-IRT team was consulted for review of this information.

The trial was an open-label, randomized, phase 1 trial of subjects with measurable and symptomatic multiple myeloma after at least one prior therapy or who was refractory to or unsuitable for bone marrow transplantation. Subjects were randomized 1:1, without

stratification, to receive bortezomib either as an IV bolus (n=12) or a subcutaneous injection (n=12) dosed at 1.3 mg/m^2 twice weekly for 2 weeks (Days 1, 4, 8, and 11), in 21 day cycles. In this trial, PK and ECG information was obtained at multiple time points on Cycle 1 Day 1. Large increase in mean QT interval (i.e., >20 ms) with 30% increase in exposure with repeated dosing is not anticipated as no significant concentration-QT relationship was identified for bortezomib.

QT-IRT recommends that following language be added to the Prescribing Information (PI).

Section 12.2:
The effect of a single dose of bortezomib 1.3 mg/m^2 following intravenous or subcutaneous administration was evaluated in an open-label, phase I study in 24 subjects with measurable and symptomatic multiple myeloma. No large changes in mean QTc interval (i.e., >20 ms) from baseline were detected. Because of the design limitations, small increase in mean QT interval (i.e., <10 ms) cannot be ruled out.

The reader is referred to the QT-IRT team review for further details.

4.4.3 Pharmacokinetics

Phase 2 studies in subjects with multiple myeloma have shown that following twice weekly IV administration of 1.0 mg/m^2 and 1.3 mg/m^2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, the mean maximum plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose.

The mean elimination half-life of bortezomib with multiple dosing ranged from 30.7 to 193 hours after the 1.0 mg/m^2 dose and 11.5 to 108 hours after the 1.3 mg/m^2 dose. The mean total body clearance was 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively.

In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post-IV dosing. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1 hour post-IV dosing was approximately 61%.

In a randomized phase 1 trial performed in 24 patients with relapsed/refractory multiple myeloma who received IV or SC injections of Velcade 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 cycles, peak plasma concentration (C_{max}) and peak enzyme inhibition (E_{max}) occurred later and were lower for SC administration relative to

IV. However, similar systemic exposure (AUC) and proteasome inhibition (AUE) for both IV and SC routes were seen. This trial will be reviewed in more detail in section 5.3.

4.5 Division of Medication Error Prevention and Analysis

The Applicant submitted the results of a Human Factors study conducted to evaluate whether Velcade would be reconstituted correctly and that users would draw up the correct dose for delivery to patients via the prescribed route (intravenous or subcutaneous).

Per the Applicant: "MPI developed a new VELCADE® packaging concept (including inserts) for the introduction of the subcutaneous route of administration using in-house staff. Once MPI independently arrived at a refined design package design, the company retained (b) (4) to conduct a pre-summative usability test (with 6 participants) and summative usability test (with 45 participants) of the product. The goal of summative usability testing is to validate that a production-equivalent design meets the intended use requirements and facilitates safe, effective user interactions. We often conduct pre-summative usability testing prior to validation testing to identify design-related use errors upfront, before investing resources in a summative test."

From the study results, the Applicant concluded that "the residual risk associated with VELCADE®'s package design is reasonably low in contrast to its benefits. Accordingly, this report claims that VELCADE®'s package provides adequate instruction to users on how to reconstitute the drug and prepare injections for intravenous and subcutaneous delivery (i.e., load a syringe with the proper, prescribed dose)."

VELCADE® will be reconstituted by hospital pharmacy personnel, including pharmacists and pharmacy technicians. It will also be reconstituted by registered nurses who work on oncology units or in private clinics.

The results of the study show that fourteen (31.1%) out of the 45 participants committed a total of one or more use errors when performing the hands-on tasks.

Per the study report, "in many cases, test participants did not bother to read the package, committed errors when performing calculations requiring simple math skills that supposedly are fundamental to working effectively in their professions. Accordingly, the summative usability test raised our concern about the some of the users' training and work habits. Although we are professionally inclined to cite design flaws as root causes of observed use errors, we could not attribute any significant use errors to the package materials presented to the user population sample."

Reviewer Comment: Human Factor and Usability testing is not required for other parenteral oncology products presently marketed. Velcade will not be reconstituted or administered by patients or caregivers. The results of this usability study do not conclude that the errors were due to flaws in the package design. In order to enhance the accuracy of drug reconstitution and administration, the Agency will request that the Applicant propose methods for communication of the proper methods of reconstitution and preparation of the Velcade for each route of administration to the health care community.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 below summarizes the clinical studies submitted by the Applicant in support of the proposed labeling changes.

Table 2 Table of Clinical Trials

Study Number/Title	Study Design	VELCADE/Dexamethasone Treatment Regimen	No. of Subjects Enrolled
Pilot Study 26866138-CAN-1004 Comparison of pharmacokinetics and pharmacodynamics of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma	Phase 1, randomized (1:1), open- label, multicenter study of the PK/PD, safety, and efficacy of SC vs. IV VELCADE in subjects with relapsed multiple myeloma after at least 1 prior therapy.	VELCADE 1.3 mg/m^2 twice weekly by IV bolus or SC injection on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 cycles (24 weeks). VELCADE concentration: 1 mg/mL for both groups Optional oral dexamethasone (20 mg daily on the day of and the day after VELCADE administration) after 2 cycles at investigator's discretion for subjects with stable disease.	24 (12 SC group/ 12 IV group)
Registration Study 26866138-MMY-3021 An open-label, randomized study of subcutaneous and intravenous VELCADE® in subjects with previously treated multiple myeloma	Phase 3, randomized (2:1), open-label, international, multicenter study comparing efficacy, safety and PK/PD of SC vs. IV VELCADE in subjects with relapsed multiple myeloma following 1 to 3 prior lines of therapy	VELCADE 1.3 mg/m^2 twice weekly by IV bolus or SC injection on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 cycles (24 weeks). VELCADE concentration: 1 mg/mL (IV) or 2.5 mg/mL (SC). Optional oral dexamethasone (20 mg daily on the day of and the day after VELCADE administration) beginning in Cycle 5 in case of NC or PR.	222 (148 SC group/ 74 IV group)

IV=intravenous; No. =number; NC=no change; PD=pharmacodynamic; PK=pharmacokinetic; PR=partial response; SC=subcutaneous

Source: Applicant submission – *Module 2; 2.5 Clinical Overview* page 13.

Reviewer comment: *These trials were adequate to support the new route of administration given the similar efficacy and safety of the IV and SC routes and the comparable PK/PD profiles of both routes of administration. Trial CAN-1004 provided PK and PD support by showing comparable PK and PD parameters for IV and SC Velcade. Trial MMY-3021 provided evidence that the Subcutaneous route efficacy was not inferior to that of the approved Intravenous route. Review of the safety data indicates that there may actually be a better adverse reaction profile for the SC route regarding the adverse event of interest, peripheral neuropathy.*

5.2 Review Strategy

Review was conducted of applicant's eCTD submission of background, trial protocol, analyses, and data, and current literature pertaining to multiple myeloma and available

treatments. The goal was to evaluate the level of evidence provided to support approval of a new subcutaneous route of administration and associated labeling claims. The raw and derived datasets submitted were analyzed using JMP.

5.3 Discussion of Individual Studies/Clinical Trials

The applicant conducted a Phase 3 randomized, open label trial, comparing the efficacy, safety, and pharmacokinetics/pharmacodynamics of subcutaneous versus intravenous Velcade in subjects with relapsed multiple myeloma following 1 to 3 prior lines of therapy (trial 26866138-MMY-3021). A phase 1 randomized, open label, trial of the pharmacokinetics/pharmacodynamics, safety, and efficacy of subcutaneous versus intravenous Velcade in subjects with multiple myeloma after at least 1 prior line of therapy (trial 26866138-CAN-1004) was also conducted. The results of these studies are reviewed individually, and where applicable, in combination, utilizing the data provided by the applicant and conducting independent analysis of the data.

Prior to conducting the pivotal phase 3 trial comparing the intravenous and subcutaneous routes of administration, the pharmacokinetics and pharmacodynamics of the two routes were evaluated in a phase 1 trial (26866138-CAN-1004). This section will provide an overview of the trial design of Trials MMY-3021 and CAN-1004 in addition to the high level results for CAN-1004.

Phase 1 Trial (26866138-CAN-1004)
Comparison of Pharmacokinetics and Pharmacodynamics of Subcutaneous versus Intravenous Administration of Bortezomib in Patients with Multiple Myeloma

The applicant conducted a phase 1 randomized, open label trial of the pharmacokinetics/pharmacodynamics, safety, and efficacy of subcutaneous versus intravenous Velcade in subjects with multiple myeloma after at least 1 prior line of therapy. This trial, “Comparison of pharmacokinetics and pharmacodynamics of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma”, was conducted in three sites in France between January 26, 2006 and February 25, 2007; the trial report was completed January 16, 2008.

Objectives
The primary objective of this trial was to characterize the pharmacokinetics of the two routes of administration.

The secondary objective was to characterize the pharmacodynamics (whole blood 20S proteasome inhibition), safety (including cardiac), and efficacy of the two routes of administration.

Subjects
Twenty-four (24) adult patients age 75 or younger were enrolled.

Subjects had symptomatic multiple myeloma stage I with one symptomatic osteolytic lesion, stage II, or stage III, and progressive disease after at least one prior therapy, having either already undergone bone marrow transplantation, or were otherwise not candidates for bone marrow transplantation, and had measurable paraprotein levels in the serum (≥1g/dL) or in the urine (≥ 0.2g/24h). The determination of diagnosis and stage of multiple myeloma were according to the Southwest Oncology Group (SWOG) and Durie-Salmon staging systems, respectively.

Main Inclusion Criteria
- Diagnosis of multiple myeloma according to the Southwest Oncology Group (SWOG) criteria
- Symptomatic multiple myeloma stage II or III according to Durie-Salmon staging system or stage I with one symptomatic osteolytic lesion - with progressive disease after at least one prior therapy and had already undergone or were not candidates for bone marrow transplantation – with a measurable levels of paraprotein in the serum (≥1g/dl) or in the urine (≥0.2g/24h)
- 75 years or younger
- Written informed consent
- Nonpregnant or nonchild-bearing females – Women (of child bearing potential) and men were to use adequate contraception for the duration of the study
- No active systemic infection or in the presence of any active systemic infection, had adequate broad-spectrum or organism-specific antibiotic coverage administered – afebrile with stable vital signs while receiving antibiotics for at least 48 hours prior to beginning the treatment with VELCADE
- Body weight of ≥50 kg and a body mass index (BMI) of ≤30 kg/m^2

Main Exclusion Criteria
- Projected life expectancy <2 months
- Eastern Cooperative Oncology Group (ECOG) performance status of > 2
- Amyloidosis
- ≥ 2 NCI grade peripheral neuropathy
- Cardiac disease - myocardial infarction history, heart failure, uncontrolled angina, clinically significant pericardial disease
- Arrhythmia, 2^{nd} degree or greater AV block or prolonged QTc interval (>0.45 seconds for males and >0.47 seconds for females) on screening electrocardiogram
- Creatinine level >200µmol/L
- Bilirubin, transaminases or Gamma glutamyl transferase (GGT) >3 times the upper normal limit
- Potassium, calcium or magnesium outside of upper or lower normal limits

- Platelet <70x10^9/L within 14 days of enrollment
- Absolute neutrophil count <1.0 x 10^9/L within 14 days of enrolment
- Use of medications that prolong QTc interval within 1 week prior to first study medication dose and during cycle 1
- Concomitant use of potent P450 (CYP) enzymes 3A and 2C19 inhibitors or inducers within 1 week prior to first study medication dose and during cycle 1
- Hypersensitivity to boron, mannitol, or bortezomib
- Use of any experimental drugs within 30 days of baseline
- Pregnancy

Trial Design/Methods

Subjects were randomized 1:1, without stratification, to receive either intravenous Velcade bolus concentration of 1mg/mL (group 1, consisting of 12 subjects) or subcutaneous Velcade injection at a concentration of 1mg/mL (group 2 consisting of 12 subjects) in the thigh or abdomen (rotating sites within each cycle).

Velcade was administered at the approved dose of 1.3 mg/m^2 body-surface area twice weekly for 2 weeks (on days 1, 4, 8, and 11), followed by a 10-day rest period (days 12 to 21) without treatment, for up to 8 cycles. Study drug was supplied in vials containing 3.5mg of lyophilized Velcade powder with 35mg mannitol USP to be reconstituted within 8 hours prior to dosing using normal sterile saline (0.9%) for a final drug concentration of 1mg/mL.

Dose modifications

The first 3 subjects in each treatment group had pharmacokinetic samples analyzed in real time and if the C_{max} or AUC of the subcutaneous treatment group subjects was high (50% or more above the expected value), the dose of Velcade in the following cycles was reduced to 1.0 mg/m^2. If the C_{max} or AUC remained high at 1.0 mg/m^2, the dose was further reduced to 0.7 mg/m^2.

Prior to each Velcade dose administration, each subject was evaluated for toxicities possibly due the previous dose(s). Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI CTCAE], Version 3.0. With the exception of neuropathic pain and peripheral sensory neuropathy, previously established or new toxicities observed any time, were managed as follows:

- For febrile neutropenia, a grade 4 hematologic toxicity or any ≥grade 3 non-hematologic toxicity considered by the investigator to be related to Velcade, the drug was to be withheld
  - For lymphopenia of any grade, dose interruption or study discontinuation was not required
- For non-hematologic toxicities, Velcade was to be withheld for up to 2 weeks until the toxicity returned to grade 1

- For hematologic toxicities, Velcade was to be withheld for up to 2 weeks until the subject had a hemoglobin value ≥7.5g/dL, an absolute neutrophil count (ANC) ≥ $0.75x10^9$/L and a platelet count ≥$50x10^9$/L

If after Velcade had been withheld, the described toxicity did not resolved as described above, the study drug was to be discontinued. If the toxicity resolved, as defined above, then Velcade was to be restarted at a dose reduced by approximately 25%, as follows:

- If the subject was receiving 1.3 mg/m², the dose was reduced to 1.0 mg/m²
- If the subject was receiving 1.0 mg/m², the dose was reduced to 0.7 mg/m²
- If the subject was receiving 0.7 mg/m², the study drug was discontinued
  - Dose reductions below 0.7 mg/m² were not allowed

Subjects who experienced VELCADE-related neuropathic pain or peripheral sensory neuropathy had dose modifications in accordance with the following algorithm:

Figure 2 Dose Modification Algorithm for Peripheral Sensory Neuropathy

Neuropathic Pain (NCI CTC Grade)		0	1	2	3	4
		Normal	Loss of deep tendon reflexes or paresthesia but not interfering with function	Objective sensory loss or paresthesia, interfering, with function, but not with ADLs	Sensory loss or parathesia interfering with ADLs	Permanent sensory loss that interferes with function
0	None	no action	no action	25% dose reduction	Hold; 50% dose reduction, schedule D required	discontinue Bortezomib
1	Mild pain not interfering with function	no action	no action	25% dose reduction	Hold; 50% dose reduction, schedule D required	discontinue Bortezomib
2	Moderate pain, pain or analgesics	25% dose reduction	50% dose reduction	Hold, 50% dose reduction	Hold; 50% dose reduction, schedule D required	discontinue Bortezomib
3	Severe pain: pain or analgesics	Hold; 50% dose reduction, schedule D required	Hold; 50% dose reduction, schedule D required	Hold; 50% dose reduction, schedule D required	discontinue Bortezomib	discontinue Bortezomib
4	Disabling	discontinue Bortezomib	discontinue Bortezomib	discontinue Bortezomib	discontinue Bortezomib	discontinue Bortezomib

Hold: Interruption of bortezomib (Velcade) for up to 2 weeks until the toxicity returns to grade 1 or better.
25% dose reduction: From 1.3 mg/m^2/dose; 50% dose reduction: From 1.3 mg/m^2/dose
Schedule D: Schedule change from bortezomib (Velcade) twice per week (Days 1, 4, 8, 11) to once per week (Days 1, 8, 15, 22); if the subject is already on once weekly schedule, then the drug would be given every other week (Day 1, 15); for patients with stable disease after 2 cycles, dexamethasone may have been added to the treatment at the discretion of investigator.

Source: Applicant submission Clinical study reports 26866138-CAN-1004 – *Module 5; 5.3.3.2.3 – Report Body* page 303.

Subject Discontinuation
Subjects were required to be discontinued for:

- Progressive disease
- Absence of sufficient evidence of antitumor efficacy and the development of recurrent drug-related grade 3 or 4 non-hematological toxicity
- Request by the subject

Subjects may have also been discontinued for:

- Subject safety (as determined by the principal investigator)
- Serious adverse event (SAE)
- Serious protocol violation

Results of Trial CAN-1004

Subject Disposition

The mean age was 60.4 years with 18 subjects (18 of 24; 75%) being less than 65 years. The arms were well-balanced for age. Of the 24 subjects enrolled in the trial, 10 (42%) were men and 14 (58%) were women. Of the 24 subjects, 17 (71%) subjects had an ECOG score of 0 and 7 subjects (29%) had a score of 1. The distribution of gender was similar between the treatment groups. Mean body surface area (BSA), height, and subject's body weight were similar between the treatment groups with mean height being 161.58 cm in the IV group and 163.75 cm in the SC group; mean body weight was 69 kg in the IV group and 71 kg in the SC group; BSA was 1.73 m^2 in the IV group and 1.76 m^2 in the SC group. See Table 3 and Table 4 for baseline characteristics and demographics of participants and subject disposition

Table 3 Demographics and Baseline Characteristics

	-------- IV ------- (N=12)	-------- SC ------- (N=12)	------ Total ------ (N=24)
Age (Years)			
N	12	12	24
Category, n (%)			
<65	9 (75)	9 (75)	18 (75)
≥65	3 (25)	3 (25)	6 (25)
Mean (SD)	60.4 (6.10)	60.4 (5.88)	60.4 (5.86)
Median	61.0	61.5	61.0
Range	(51;71)	(49;71)	(49;71)
Gender, n (%)			
N	12	12	24
Male	3 (25)	7 (58)	10 (42)
Female	9 (75)	5 (42)	14 (58)
Weight (kg)			
N	12	12	24
Mean (SD)	69.25 (12.484)	71.25 (16.499)	70.25 (14.344)
Median	72.00	67.00	69.50
Range	(50.0;88.0)	(47.0;97.0)	(47.0;97.0)
Height (cm)			
N	12	12	24
Mean (SD)	161.58 (9.681)	163.75 (9.440)	162.67 (9.416)
Median	158.50	164.00	160.00
Range	(152.0;180.0)	(145.0;176.0)	(145.0;180.0)
Body Surface Area (m^2)			
N	12	12	24
Mean (SD)	1.73 (0.188)	1.76 (0.237)	1.74 (0.210)
Median	1.70	1.73	1.72
Range	(1.4;2.1)	(1.4;2.1)	(1.4;2.1)
ECOG Performance Status, n (%)			
N	12	12	24
0: Asymptomatic	9 (75)	8 (67)	17 (71)
1: Symptomatic, Fully Ambulatory	3 (25)	4 (33)	7 (29)

ECOG = Eastern Cooperative Oncology Group
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Source: Applicant submission Clinical study reports 26866138-CAN-1004 – *Module 5; 5.3.3.2.3 – Report Body* page 34.

Of the 24 subjects, 54% had IgG myeloma and 58% had stage III disease.

> **Reviewer comment:** *Demographic and baseline characteristics of subjects were comparable between the IV and the SC treatment groups and were well balanced.*

Table 4 Subject Disposition

Category Reason	IV (N=12) n (%)	SC (N=12) n (%)	Total (N=24) n (%)
ITT Population[a]	12 (100)	12 (100)	24 (100)
Safety Population[b]	12 (100)	12 (100)	24 (100)
PK/PD Evaluable Population	10 (83)	10 (83)	20 (83)
Subjects Who Completed Study Treatment	4 (33)	5 (42)	9 (38)
Subjects Who Discontinued from Study Treatment	8 (67)	7 (58)	15 (63)
DISEASE PROGRESSION	1 (8)	3 (25)	4 (17)
LACK OF TREATMENT EFFICACY	1 (8)	0	1 (4)
MAJOR PROTOCOL DEVIATION	0	1 (8)	1 (4)
NON HEMATOLOGIC TOXICITY ≥ 3	3 (25)	3 (25)	6 (25)
SERIOUS ADVERSE EVENT NO.	1 (8)	0	1 (4)
OTHER	2 (17)	0	2 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
[a] ITT population is defined as all randomized subjects.
[b] Safety population is defined as subjects who received at least one dose of study drug.
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Source: Applicant submission Clinical study reports 26866138-CAN-1004 – *Module 5; 5.3.3.2.3 – Report Body* page 33.

There were 9 inclusion/exclusion criteria violations reported for 8 subjects, including:

- Life expectancy <2 months (1 subject)
- Weight <50 kgs or BMI >30 (3 subjects)
- Use of experimental drugs within 30 days (1 subject)
- There were 4 violations of “not applicable” or no answer to the questions regarding “adequate birth control” (4 subjects)
- In addition, a drug disposition violation (administration of IV doses on cycle 1 day 8 and cycle 1 day 11) in one patient in the SC arm, resulted in early withdrawal from the study
- The subject was not excluded by the applicant from the analysis and was analyzed in the SC treatment group

Of the twenty-four subjects that were enrolled in trial CAN-1004 and randomized to receive bortezomib (Velcade) as IV bolus (n=12) or SC injection (n=12) on days 1, 4, 8 and 11 who had samples drawn immediately prior to and after the dose administered on day 1 and day 11, 4 subjects, 2 from each treatment group, were not considered PK-evaluable and were excluded from the PK and PD analyses. One subject from the IV group and one subject from the SC group did not complete scheduled PK sampling on day 11. One subject had blood for PK sampling drawn from the same arm as the IV dose was administered on day 1. One subject in the SC arm underwent dose reduction to 1 mg/m^2 on day 8. A 2-minute sample (0.03 hour) taken on day 11 from a subject in the SC group was taken prior to the dose and that sample (from day 11) was thus not included in the analysis. Thus 20 subjects (10 per treatment group comprised the PK-evaluable population; the safety population consisted of the 24 subjects enrolled (12 per treatment group).

Efficacy (CAN-1004)
The primary objective of this trial was characterization of the pharmacokinetics of the the two routes of bortezomib administration (new SC route of administration compared to the approved IV route). To that end, efficacy results from trial CAN-1004 from the 20 patients evaluable for PK and PD analysis showed comparable exposure with SC and IV routes of administration of bortezomib. Plasma AUCs were similar after both single dose and repeat dose administration in both groups as were PD parameters (T_{max}, E_{max}, and AUE) as calculated by percent inhibition of 20S proteosome activity-time data (change in proteosome activity from baseline). The mean maximum proteosome inhibition (E_{max}) and AUE_{0-27}) were comparable following IV and SC administration of bortezomib. C_{max} after SC administration was lower than after IV administration.

The mean observed maximum percent inhibition of 20S proteasome activity (relative to baseline) in whole blood following administration of bortezomib ranged from 60.1% to 86.5% and from 33.4% to 77.7% for the IV and SC groups, respectively. After multiple doses on day 11, the average maximum percent inhibition of 20S proteasome activity (relative to baseline) observed following administration of the drug was 68.8% and 57.0% for the IV and SC groups, respectively.

This was a PK/PD trial and not designed or adequate to establish efficacy. Efficacy was a secondary endpoint. Five subjects (5/12; 42%) in the IV group and 7 subjects (7/12; 58%) in the SC group had a response of CR, VGPR, or PR, which included 2 subjects with a response of CR, 1 in each treatment group, and 5 subjects with a response of VGPR, 3 in the IV treatment group and 2 in the SC group.

For a more detailed review of PK/PD studies, please see Clinical Pharmacology Review for NDA 21602 for this Supplement (S-27).

Safety (CAN-1004)
Safety was a secondary objective of this PK/PD trial. The safety profile was similar between the IV and SC groups and also similar to that seen in previous studies with the same patient population. No new safety signals were identified for the SC route of administration in this trial.

Of the 24 subjects, 96% subjects had a drug-related treatment emergent adverse event (TEAE). Twelve subjects (100%) in the IV group and 11 subjects (92%) in the SC group experienced at least 1 AE (all reported as related to Velcade). The most frequent adverse events in both the SC and IV treatment groups were blood and lymphatic system disorders – anemia (50% in both groups); neutropenia (33% in SC and 67% in IV); thrombocytopenia (33% in SC and 25% in IV); and leukopenia (50% in SC and 33% in IV). Gastrointestinal disorders occurred in 67% of patients receiving SC and 75% in those receiving IV. GI disorders included: diarrhea (33% in SC and 58% in IV), nausea (33% in SC and 42% in IV), and vomiting (33% in SC and 25% IV). Neuropathy was commonly occurring at 58% in both treatment groups, however peripheral sensory

neuropathy was numerically less at 8% in SC and 17% in IV. Asthenia occurred in 58% of patients receiving SC and 67% of patients receiving IV).

Nine subjects (75%) in the IV group and 7 subjects (58%) in the SC group experienced at least 1 grade 3 or greater AE (severe), with the most common ≥grade 3 event being blood and lymphatic system disorders. Overall, 6 subjects of the 24 (25%) experienced an SAE; 5 (42%) of these subjects in IV group experienced an SAE, 2 of which were considered related to Velcade; 1 subject in the SC group (8%) experienced an SAE, which was considered related to Velcade. There were no deaths reported in this trial.

Overall, 8 subjects (33%) discontinued Velcade due to an AE. Half of the 12 subjects in the IV group and 2 subjects (17%) in the SC group discontinued due to an AE. The most common reason for discontinuation was nervous system disorders (5/24; 21%). Most hematologic toxicities were ≤ grade 2, without notable differences were observed between the IV and SC treatment groups for the incidence of high grade hematology toxicities. A grade ≥3 hemoglobin decrease was reported in 1 subject in each treatment group; grade ≥3 platelet decrease and lymphocyte decrease were reported in 2 subjects in each treatment group; a grade ≥3 WBC decrease was reported in 3 subjects in each treatment group. A grade ≥3 neutropenia was reported in 7 subjects in the IV group and 2 subjects in the SC group. For each serum chemistry parameter, most subjects had an on trial worst toxicity ≤Grade 2 in intensity. No notable differences in the serum chemistry toxicity grades were observed between the 2 treatment groups.

Eleven subjects (92%) of the 12 subjects administered SC Velcade experienced a reaction at the site of drug administration (erythema).

Post-baseline changes for QTcB and QTcF were less than 30 msec in all subjects at all time points (5 min, 15 min, 30 min, 60 min, 2h, 4h, 6h and 10h post Velcade administration) evaluated. However, one subject on the SC group had an absolute QTcB and QTcF of ≤480 msec at every time point; however, this subject had an elevated QTcB and QTcF measurement at baseline. No clinically relevant increase in the mean QTcB or QTcF after Velcade dosing was observed at any time point in either of the treatment groups.

Table 5 below, provides an overview of adverse events. Table 6 provides a summary of the TEAEs that were reported at a differential rate of ≥10%. Severe (grade 3 & 4) adverse reactions are described in Table 7.

Table 5: Incidence of Adverse Reactions Trial CAN-1004

	iv (N=12)	sc (N=12)
Number of subjects with		
Any adverse event	12 (100)	11 (92)
Related adverse events	12 (100)	11 (92)
Any serious adverse event	5 (42)	1 (8)
Related serious adverse events	2 (17)	1 (8)
Grade ≥3 toxicity adverse events	9 (75)	7 (58)
Related grade ≥3 toxicity adverse events	8 (67)	6 (50)
Adverse events causing discontinuation of study drug	6 (50)	2 (17)
Related adverse events causing discontinuation of study drug	4 (33)	2 (17)
Number of subjects who died due to adverse event	0	0

Source: Applicant submission Clinical study reports 26866138-CAN-1004 – *Module 5; 5.3.3.2.3 – Report Body* page 53.

Table 6 Treatment Emergent Adverse Events with Differential Incidence of at Least 10% Between Arms of Trial CAN-1004

Treatment Emergent AE MedDRA SOC and Preferred Term	Subcutaneous All Grades (N=12) N (%)	Intravenous All Grades (N=12) N (%)
Total No. subjects with TEAE	11 (92)	12 (100)
Blood and Lymphatic Disorders	9 (75)	9 (75)
Leukopenia	6 (50)	4 (33)
Neutropenia	4 (33)	8 (67)
Pancytopenia	0	1 (8)
Thrombocytopenia	4 (33)	3 (25)
Gastrointestinal Disorders	8 (67)	9 (75)
Constipation	3 (25)	1 (8)
Diarrhea	4 (33)	7 (58)
General Disorders and Administration Site Conditions	7 (58)	10 (83)
Asthenia	7 (58)	8 (67)
Peripheral Edema	2 (17)	0
Infections and Infestations	6 (50)	7 (58)
Acute Tonsillitis	0	2 (17)

Treatment Emergent AE MedDRA SOC and Preferred Term	Subcutaneous All Grades (N=12) N (%)	Intravenous All Grades (N=12) N (%)
Bronchitis	2 (17)	0
Rhinitis	2 (17)	0
Musculoskeletal and Connective Tissue Disorders	3 (25)	8 (67)
Bone Pain	0	3 (25)
Pain in Extremity	0	2 (17)
Torticollis	0	2 (17)

Source: Reviewer Generated Table From Review of Raw Datasets

Table 7 Treatment Emergent Grade 3-4 Adverse Reactions

MedDRA SOC Preferred Term	SC Grades 3-4 n=12 (%)	IV Grades 3-4 n=12 (%)
Blood and Lymphatics		
Anemia	1 (8)	1 (8)
Leukopenia	1 (8)	1 (8)
Neutropenia	2 (17)	6 (50)
Pancytopenia	0	1 (8)
Thrombocytopenia	3 (25)	3 (25)
Cardiac Disorders		
Atrial Fibrillation	0	1 (8)
Cardiac Failure	0	1 (8)
General Disorders and Administration Site Conditions		
Hyperthermia	1 (8)	0
Infections and Infestations		
Pneumonia	1 (8)	0
Metabolism and Nutrition Disorders		
Anorexia	0	1 (8)
Hyperglycemia	0	1 (8)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	0	1 (8)
Bone Pain	0	1 (8)
Nervous System Disorders		
Neuropathy	2 (17)	1 (8)
Peripheral Sensory Neuropathy	0	1 (8)
Syncope	0	1(8)
Tremor	1 (8)	0
Respiratory, Thoracic, and Mediastinal Disorders		

Dyspnea Exertional	0	1 (8)
Respiratory Failure	0	1 (8)
Surgical and Medical Procedures		
Osteosynthesis	0	1 (8)

Source: Modified from applicant submission Clinical study reports 26866138-CAN-1004 – *Module 5; 5.3.3.2.3 – Report Body* pages 59-61

Table 8 below summarizes serious adverse reactions reported during the trial.

Table 8 Serious Adverse Reactions

MedDRA System Organ Class Preferred Term	IV (N=12) n (%)	SC (N=12) n (%)	Total (N=24) n (%)
Total no. subjects WITH TEAE	5 (42)	1 (8)	6 (25)
Cardiac disorders	1 (8)	0	1 (4)
Atrial fibrillation	1 (8)	0	1 (4)
Infections and infestations	1 (8)	0	1 (4)
Herpes zoster	1 (8)	0	1 (4)
Musculoskeletal and connective tissue disorders	1 (8)	0	1 (4)
Back pain	1 (8)	0	1 (4)
Nervous system disorders	1 (8)	1 (8)	2 (8)
Neuropathy	0	1 (8)	1 (4)
Syncope	1 (8)	0	1 (4)
Respiratory, thoracic and mediastinal disorders	2 (17)	0	2 (8)
Dyspnoea exertional	1 (8)	0	1 (4)
Respiratory failure	1 (8)	0	1 (4)
Surgical and medical procedures	1 (8)	0	1 (4)
Osteosynthesis	1 (8)	0	1 (4)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Source: Applicant submission Clinical study reports 26866138-CAN-1004 – *Module 5; 5.3.3.2.3 – Report Body* page 63.

Reviewer comment: *Although the number of subjects in this PK/PD study are small, the safety data and incidence and types of common adverse events appear consistent with those of the pivotal study which will be discussed below and in sections 6 and 7 of this review.*

Phase 3 Pivotal Trial (26866138-MMY-3021)

An Open-Label, Randomized Study of Subcutaneous and Intravenous VELCADE® in Subjects with Previously Treated Multiple Myeloma

Following the discussion of the trial design of the pivotal phase 3 trial, MMY-3021, *Sections 6 and 7* below will focus on efficacy and safety review of the data from this pivotal trial.

Trial Design
The pivotal trial in support of a new subcutaneous route of administration for bortezomib was a phase 3, open label, randomized, international (ex-US) trial comparing the efficacy and safety of the proposed subcutaneous route of administration to the approved intravenous route in patients with previously treated multiple myeloma (who had not been previously treated with Velcade). The trial ran from 07/16/08 through 08/31/10.

A total of 222 subjects were enrolled and randomized in a 2:1 ratio to receive 1.3 mg/m^2 Velcade by either SC or IV injection (148 in SC arm and 74 in IV arm) in this open label, multicenter, international trial. Subjects were stratified and randomly assigned to treatment by means of an interactive voice response system (IVRS).They were stratified by the number of lines of prior therapy (1 versus >1) and International Staging System (ISS) stage (stages I, II, or III) incorporating beta$_2$-microglobulin and albumin levels, two well-established independent prognostic factors in untreated multiple myeloma and major contributors to tumor stage determination. The Table 9 below summarizes staging based on serum beta$_2$-microglobulin and albumin levels (per ISS).

Table 9 Stages As Defined by ISS - Serum Beta2-Microglobulin and Albumin Levels

	Serum Albumin	
Serum β_2M	≥3.5 g/dL	<3.5 g/dL
<3.5 mg/L	Stage I	Stage II
≥3.5 mg/L to <5.5 mg/L	Stage II	Stage II
≥5.5 mg/L	Stage III	Stage III

Source: Applicant submission Clinical Trial Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 2710.

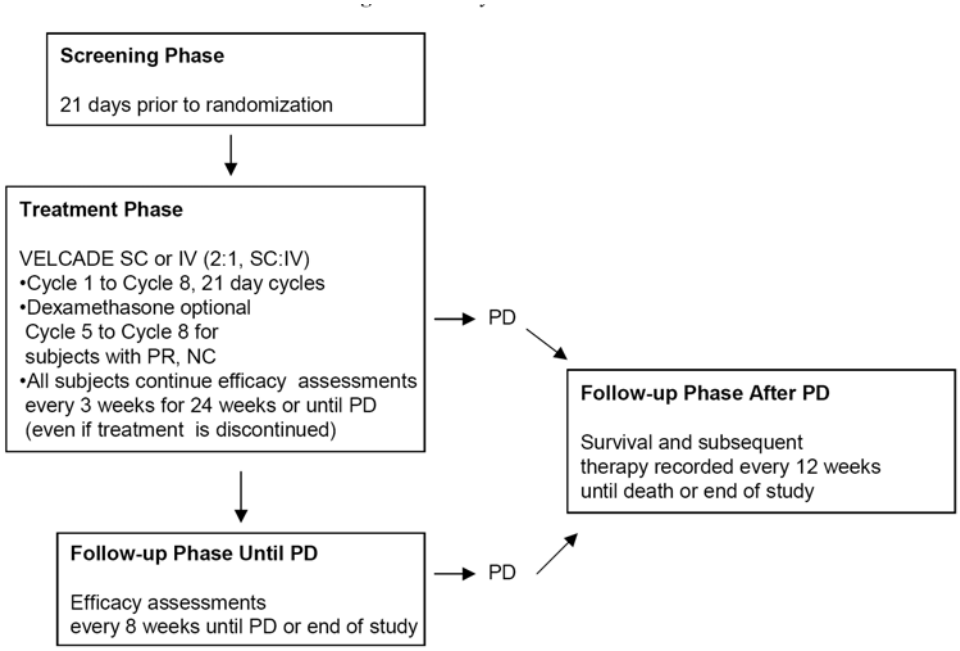
During the 24 week open label treatment phase Velcade was administered on days 1, 4, 8, and 11 of a 3-week cycle for 8 cycles. An additional 4 cycles could be given if no response was achieved after 4 cycles (for a total of up to 12 cycles of treatment) +/- dexamethasone (20 mg oral dose on the day of and day after each bortezomib administration). Additional 2 cycles could be administered for subjects with stable

disease or PR as best overall response at end of cycle 8, if evolving steadily to a late PR or CR.
During the 1-year post treatment follow up phase (1 year after the last subject was randomized) subjects who had not progressed were assessed every 8 weeks until disease progression. After disease progression, subjects were followed every 12 weeks for survival and subsequent therapies.

Oral dexamethasone could be administered in conjunction with Velcade only after the 4th cycle (i.e. starting cycle 5) if no response achieved to single-agent Velcade (in order to avoid confounding the primary endpoint analysis).

Velcade SC and IV were administered only at the investigational site and could not be self administered by the subject.

Figure 3: Trial MMY-3021 Schema



Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 2705.

Adult males and females with previously treated, relapsed, or progressive multiple myeloma consenting to trial participation were eligible for entry according to the following eligibility criteria:

All inclusion and exclusion criteria are listed in detail, below:

Inclusion

1. Men or women aged 18 years or older
2. Diagnosis of multiple myeloma based on the standard criteria
3. Measurable, secretory multiple myeloma defined as serum monoclonal immunoglobulin G (IgG) of ≥10 g/L, serum monoclonal immunoglobulin A (IgA) or immunoglobulin E (IgE) of ≥5 g/L, or serum monoclonal immunoglobulin D (IgD) of ≥0.5 g/L; or urine M-protein of ≥200 mg/24 hours
4. Relapse or progression of myeloma following prior systemic antineoplastic therapy. Relapse or progression was defined by any of the following: 1) Reappearance of measurable disease (as defined above) following CR 2) ≥25% increase in serum or urine M-protein 3) Development of new or worsening lytic bone disease 4) New plasmacytomas or ≥50% increase in the longest dimension of an existing plasmacytoma 5) Worsening hypercalcemia (corrected serum calcium >11.5 mg/dL [2.8 mmol/L]) secondary to multiple myeloma
5. KPS score ≥70%
6. Platelet count ≥50 x 109/L without transfusion support within 7 days before the laboratory test
7. Hemoglobin ≥8 g/dL (≥4.96 mmol/L) without transfusion support within 7 days before the laboratory test
8. Absolute neutrophil count (ANC) ≥0.75 x 10^9/L
9. Corrected serum calcium <14 mg/dL (<3.5 mmol/L)
10. Aspartate aminotransferase (AST) ≤2.5 times upper limit of normal (ULN)
11. Alanine aminotransferase (ALT) ≤2.5 times ULN
12. Total bilirubin ≤1.5 times ULN (except in subjects with congenital bilirubinemia, such as Gilbert syndrome)
13. Creatinine clearance ≥20 mL/min
14. Toxic effects of previous therapy or surgery had resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 3.0) Grade 1 or better
15. Women who were not postmenopausal or surgically sterile were to have had a negative pregnancy test and were to have agreed to use an acceptable method of birth control during the study until 30 days after the last dose of drug.
16. Men were to have agreed to not father a child and to use a latex condom during treatment and for 30 days after the last dose of study drug, even if they had had a successful vasectomy, if their partners were of childbearing potential.
17. Voluntary written informed consent was to be given before performance of any study-related procedure not part of normal medical care, with the understanding that consent could be withdrawn by the subject at any time without prejudice to future medical care.

Exclusion

1. Previous treatment with Velcade

2. More than 3 previous lines of therapy (separate lines of therapy were defined as single or combination therapies that were either separated by disease progression or by a >6 month treatment-free interval)
3. Peripheral neuropathy or neuropathic pain of NCI CTCAE Grade ≥2
4. Any of the following within 3 weeks before randomization: antineoplastic or experimental therapy, corticosteroid use above 10 mg/day (prednisone or equivalent), or plasmapheresis
5. Either radiation therapy or major surgery (kyphoplasty was not considered major surgery) within 2 weeks before randomization
6. Prior malignancy other than multiple myeloma diagnosed or treated within the previous 2 years, with the exception of completely resected carcinoma in situ or basal/squamous carcinoma of the skin
7. Myocardial infarction within 6 months before enrollment or New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or clinically significant conduction system abnormalities
8. Concurrent medical condition or disease (e.g., active systemic infection, uncontrolled diabetes, pericardial disease, acute diffuse infiltrative pulmonary disease, therapeutic use of anticoagulants) that was likely to interfere with study procedures or results (including local injection tolerability), that in the opinion of the investigator would have constituted a hazard for participating in the study
9. History of allergic reaction attributable to dexamethasone or its constituents, or compounds containing boron or mannitol

Objectives

The primary objective of the trial was non-inferiority of SC compared to IV bortezomib in overall response rate (ORR) after four cycles of treatment in all patients with diagnosis of measurable, secretory multiple myeloma who received one or more dose of drug (response-evaluable population), with non-inferiority defined as retention of 60% of the IV (active) treatment effect (as measured by ORR).

The secondary objectives of the trial were:

- Determination of CR, near complete response, and very good partial response rates after 4 cycles of single-agent Velcade
- ORR after 8 cycles including the effect of adding dexamethasone
- Duration of response
- Time to disease progression
- Progression-free survival
- One-year survival
- Time to response following administration of either IV or SC
- Evaluation of safety and tolerability of the 2 routes of administration, including the local tolerability of SC administration

- Description of the plasma pharmacokinetics and pharmacodynamics (by whole blood 20S proteasome inhibition assay) of SC administered compared with IV administered Velcade

The exploratory objectives were:

- Assessment of resource utilization (MRU), including the use of injection supplies (i.e., IV access devices, associated supplies and infusion solutions)
- Determination of the feasibility of detecting baseline proteasome activity levels in bone marrow in a subset of subjects

Dosing

IV Velcade for Injection was prepared by reconstitution with 3.5 mL of normal saline, injection for bortezomib concentration of 1 mg/mL. SC Velcade for Injection was prepared by reconstitution with 1.4 mL of normal saline injection for bortezomib concentration of 2.5 mg/mL.

Velcade was administered on days 1, 4, 8, and 11 of a 3-week cycle for 8 cycles. Additional 4 cycles could be given if no response was achieved after 4 cycles (for a total of up to 12 cycles of treatment) +/- dexamethasone (20 mg oral dose on the day of and day after each bortezomib administration). Additional 2 cycles could be administered for subjects with stable disease or PR as best overall response at end of cycle 8, if evolving steadily to a late PR or CR.

Dose Modification

Velcade Dose Modification for Hematological Toxicity

If platelet count was < 30 x 10^9/L, or hemoglobin concentration was <8 g/dL (<4.96 mmol/L) (previous RBC transfusion, or recombinant human erythropoietin use was allowed), or if ANC <0.75 x 10^9/L, Velcade dose was skipped and not made up during the cycle.

Velcade Dose Modification for Non-hematological Toxicity

If a subject experienced any grade 3 or 4 non-hematologic toxicity considered by the investigator to be related to Velcade, Velcade was to be held until the toxicity returned to grade 1 or baseline. After recovery of the toxicity to a level allowing continuation of therapy, Velcade was to be administered at a reduced dose.

Only two dose reductions were permitted for Velcade (from 1.3 mg/m^2 to 1 mg/m^2 and from 1 mg/m^2 to 0.7 mg/m^2). If major local SC injection site reactions were observed after completion of cycle 1, a less concentrated Velcade solution (1 mg/mL instead of 2.5 mg/mL) could have been administered instead of a dose reduction for subjects in the SC treatment group if, in the investigator's opinion, this was deemed to improve local tolerability.

Cycles could be delayed for a maximum of 2 weeks. Doses required to be held were skipped and not made up later in the cycle.

On the first day of any cycle the following parameters were to be met in order to start a new cycle:

- Platelet count ≥50 x 10^9/L
- Hemoglobin ≥8 g/dL (≥4.96 mmol/L) (prior RBC transfusion or recombinant human erythropoietin use was allowed)
- ANC ≥0.75 x 109/L
- Non-hematologic toxicity must have recovered to Grade 1 or baseline

Figure 4 below describes the dose modification plan for Velcade-related neuropathy.

Figure 4 Dose Modification Schema for Neuropathy

NeuropathicPain (NCI CTCAE Grade [Version 3.0])		0	1	2	3	4
		Normal	Asymptomatic; Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling) interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling
0	None	No action	No action	*Reduction by 1 dose level*	**Hold; reduction by 2 dose levels; schedule Δ required**	Discontinue VELCADE
1	Mild pain not interfering with function	No action	No action	*Reduction by 1 dose level*	**Hold; reduction by 2 dose levels; schedule Δ required**	Discontinue VELCADE
2	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	*Reduction by 1 dose level*	*Reduction by 2 dose levels*	**Hold**; *reduction by 2 dose levels*	**Hold; reduction by 2 dose levels; schedule Δ required**	Discontinue VELCADE
3	Severe pain: pain or analgesics severely interfering with ADL	**Hold; reduction by 2 dose levels; schedule Δ required**	**Hold; reduction by 2 dose levels; schedule Δ required**	**Hold; reduction by 2 dose levels; schedule Δ required**	Discontinue VELCADE	Discontinue VELCADE
4	Disabling	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE

ADL = activities of daily living
Hold = Interrupt VELCADE until the toxicity returns to Grade 1 or better.
Schedule Δ Required = Schedule change from VELCADE twice weekly (Days 1, 4, 8, 11) to once weekly (Days 1, 8) required.
For subjects previously treated with 1.3 mg/m^2 of VELCADE, "reduction by 1 dose level" means reduction to 1 mg/m^2 of VELCADE, and "reduction by 2 dose levels" means reduction to 0.7 mg/m^2 of VELCADE (+ schedule Δ if indicated by the table). For subjects previously treated with 1 mg/m^2 of VELCADE, "reduction by 1 dose level" means reduction to 0.7 mg/m^2 of VELCADE; in case of "reduction by 2 dose levels" a reduction to 0.7 mg/m^2 of VELCADE always combined with a schedule Δ should be applied. For subjects previously treated with 0.7 mg/m^2 of VELCADE, in case of "reduction by 1 dose level" and "reduction by 2 dose levels" a schedule Δ should be applied.

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 2715.

Hepatotoxicity

If a subject experienced grade 3 or grade 4 non-drug-related hepatic function impairment, Velcade was to be held until recovery to grade 1 or baseline. Dose reduction was not necessary upon recovery of the toxicity to a level allowing continuation of therapy.

Dexamethasone Dose Modification

Gastrointestinal, cardiovascular, neurological, musculoskeletal, metabolic toxicities of dexamethasone led to dose modification and the necessary supportive therapies as outlined and summarized in **Error! Reference source not found.** below. Other dexamethasone related toxicities required holding dexamethasone for up to 2 weeks until the toxicity resolved to grade 1 or baseline. The dose was to be decreased from 20 mg to 8 mg to 4 mg if the toxicity was a grade 3 or higher dexamethasone-related toxicity.

Table 10 Dexamethasone Dose Modification Schema

Body Area	Event	Modification
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with histamine-2 blocker, sucralfate, or proton pump inhibitor. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	>Grade 3(requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease 1 dose level of current dose alone with concurrent therapy with histamine-2 blockers, sucralfate, or proton pump inhibitor. If symptoms persist despite above measures, discontinue dexamethasone, and do not resume.
	Acute pancreatitis	Discontinue dexamethasone, and do not resume.
Cardiovascular	Edema >Grade 2 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. If symptoms persist despite second reduction, discontinue dexamethasone, and do not resume.
Neurological	Confusion or mood alteration >Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone dose until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone, and do not resume.
Musculoskeletal	Muscle weakness >Grade 1 (symptomatic and interfering with function ± interfering with activities of daily living)	Decrease dexamethasone dose by 1 dose level. If weakness persists despite above measures, decrease dose by 1 dose level. If symptoms persist, discontinue dexamethasone, and do not resume.
Metabolic	Hyperglycemia >Grade 3 or higher	Treat with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until glucose is satisfactory.

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 2717.

Table 11 lists the assessment and monitoring schedule and Table 12 lists the schedule for the PK/PD sampling in trial MMY-3021.

Table 11 Assessments and Monitoring

Procedures	Screening[a] Days -21 to -1	Treatment Cycle, Cycle 1 to Cycle 8 Day 1[b]	Day 4	Day 8	Day 11	End-of-Treatment[c]	Follow-up[d] until PD	Follow-up[e] after PD
Informed consent	X							
Informed consent for PGx	X							
Randomization		X[aa]						
Medical history	X							
Pregnancy test	X[f]							
ECG	X[g]							
Echocardiogram	X[bb]							
Chest X-ray (PA and lateral)	X[g]							
Blood sample for PGx		X[h]						
Height (at screening only) and Weight	X	X				X		
Complete physical examination	X	X[i]				X		
BSA for dose calculation		X[j]						
Karnofsky Performance Status	X	X				X		
Neurotoxicity-directed questionnaire	X	X				X		
Vital signs [k]	X	X				X		
Serum chemistry [l]	X	X[n]				X	X	
Hematology [m]	X	X[n]	X[o]	X[o]	X [o]	X		
Assessment of Local Tolerability		X[p]	X[p]	X[p]	X[p]			
MRU data[q]		Ongoing from first dose of study treatment						
Concomitant medications, supportive therapy	Continuous from the time the ICF is signed through 30 days after last dose of study drug							
Adverse event collection	Continuous from the time the ICF is signed through 30 days after last dose of study drug							
Response Assessments								
Serum β_2-microglobulin and albumin[r]	X							
Skeletal survey	X[s]							
Assessments of extramedullary plasmacytomas (radiology or physical examination)	X[t]	X[t]				X[t]	X[t]	
Investigator assessment of response/PD		X[u]				X	X	
Blood sample for quantitative serum immunoglobulins, SPEP, serum immunofixation, serum Freelite chain[r], bone-specific AP[z]	X	X[v]				X[v]	X[v]	
24 hour urine collection for UPEP and urine immunofixation[r]	X	X[v]				X[v]	X[v]	
Bone marrow aspirate and biopsy for morphology and cytogenetics	X[w]	BM for morphology; performed only to confirm CR or if indicated due to suspicion of PD						
Long-term Follow-up								
Subsequent anti-neoplastic therapy								X
Survival								X
Study Drug Administration								
VELCADE[g]		X	X	X	X			
Dexamethasone		X[x]	X[x]	X[x]	X [x]			
Pharmacokinetic/Pharmacodynamic Substudy								
Blood for PK measurement		X[y]			X[y]			
Blood for PD measurement		X[y]			X[y]			

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; AP = alkaline phosphatase; BSA = body surface area; ECG = electrocardiogram; eCRF = electronic case report form; ICF = informed consent form; MRU = medical resource utilization; PD = progressive disease; PR = partial response; SAE = serious adverse event; NC = no change in disease; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

[a] Evaluations during the screening period are to be conducted within 21 days prior to the first dose of study drug. Bone marrow may be collected within 28 days prior to the first dose of study drug.

[b] Cycle 1 Day 1 is baseline. All baseline evaluations/procedures are to be performed within 72 hours prior to the first dose of study drug. Procedures conducted during the Screening period that are performed within 72 hours of C1D1 can also be used as the baseline evaluation and do not need to be repeated.

[c] End of treatment visit is to occur 30 days (+ 10 days) after the last dose of study drug.

[d] For subjects who discontinue study drug before disease progression and before completion of the 24 weeks of treatment in the Open-label, Treatment Phase, post treatment assessments should continue every 3 weeks (serum quantitative immunoglobulins, serum and 24-hour urine M-protein assessments, and serum calcium corrected for albumin every 3 weeks; and radiology for extramedullary plasmacytomas every 6 weeks) for the remainder of the 24 weeks after the date of randomization, then every 8 weeks thereafter. For subjects who complete the 24 weeks of treatment in the Open-label Treatment Phase before disease progression, posttreatment visits will be performed every 8 weeks. After disease progression is documented, subsequent treatment and survival status will be documented at least every 12 weeks.

[e] Follow-up will be every 12 weeks (± 1 week) from the occurrence of PD until death or until the study ends 1 year after the last subject was randomized.

[f] Women of child-bearing potential only (urine or serum).

[g] Results of tests obtained prior to signing of the informed consent as part of the subject's standard care can be used for this study if performed within 21 days before randomization. May be repeated during the study as clinically indicated.

[h] A 10-mL blood sample will be collected only for those subjects who gave informed consent for the pharmacogenomic component of this study. Participation in the pharmacogenomic component of the study is optional.

[i] Brief, symptom-focused physical examination.

[j] BSA will be calculated on Day 1 of each cycle and at subsequent visits if the subject experiences a >5% change in body weight from the most recent BSA calculation.

[k] Vital signs include heart rate, systolic and diastolic blood pressure, and temperature.

[l] Serum chemisty includes: at screening: BUN/urea, serum creatinine, sodium, potassium, chloride, bicarbonate, glucose, uric acid, total bilirubin, alkaline phosphatase, AST, ALT, and calcium; during treatment: BUN/urea, serum creatinine, sodium, potassium, glucose, albumin, total bilirubin, alkaline phosphatase, AST, ALT, and calcium; during follow-up: calcium, albumin.

[m] Hematology includes hematocrit, hemoglobin, white blood cell count, ANC, and platelet count.

[n] Must be within 72 hours prior to dose on Day 1 of Cycle 1; 24 hours prior to dose on Day 1 of subsequent cycles.

[o] Must be within 24 hours prior to dose.

[p] The location of each SC injection will be recorded. Data regarding local tolerability will be collected in Cycle 1 only, 2-4 hours after administration of study drug.

[q] MRU data will relate to the diagnosis, evaluation, and treatment of any complications resulting from the route of administration.

[r] To be analysed by the central laboratory. Only 1 serum and 1 24-hour urine sample is required by the central laboratory to perform quantitative immunoglobulin, SPEP, UPEP, and serum and urine immunofixation testing

[s] Skeletal survey performed using roentgenography at screening. Results of tests obtained prior to signing of the informed consent as part of the subject's standard care can be used for this study if performed within 21 days before randomization. If there are signs or symptoms suggesting increased or new bone lesions, radiographs of affected areas should be repeated as needed to evaluate for disease progression.
[t] CT scan or MRI should be obtained at screening for suspected extramedullary disease. If extramedullary disease is documented, a MRI or CT scan should be performed every 6 weeks (every other cycle) to document response or disease progression using the same imaging modality as used at screening, even if subjects have discontinued study medications, until PD or until 24 weeks after randomization for subjects who discontinued early. Assessments every 8 weeks thereafter. The same diagnostic test as used at baseline may be repeated at any time if indicated due to suspicion of new plasmacytomas.
[u] Beginning with Cycle 2.
[v] Not necessary on Cycle 1, Day 1 if blood and 24-hour urine samples collected during screening were within 14 days of Cycle 1, Day 1. Samples will continue to be collected every 3 weeks from all subjects, even if subjects have discontinued study medications, until PD or until 24 weeks after randomization for subjects who discontinued early. Assessments every 8 weeks thereafter. If this test is the basis for the evidence of PD, then this evaluation is to be confirmed by a second measurement 1 to 3 weeks later.
[w] Bone marrow aspirate for cytogenetics and morphology is to be collected at screening or baseline (within 28 days of first dose of study drug). Assessment will be performed locally. For cytogenetic evaluation either metaphase or FISH analysis is acceptable. For subjects who participate in the pharmacokinetic/pharmacodynamic portion of the study and have given consent, up to 2 mLs of additional bone marrow will be collected to determine the feasibility of detecting proteasome inhibition in these samples.
[x] Dexamethasone may be added, at the investigator's discretion, after Cycle 4. Dexamethasone will be orally administered on Days 1, 2, 4, 5, 8, 9, 11, & 12 of Cycle 5 to Cycle 8.
[y] For subjects who participate in the pharmacokinetic/pharmacodynamic portion of the study, a 5mL blood sample (3mL for pharmacokinetic measurements and 2mL for pharmacodynamic measurements) will be collected in Cycle 1 only, predose on Day 1 and at the sampling times listed in the following schedule on Day 11.
[z] Bone-specific alkaline phosphatase will be analyzed by the central laboratory.
[aa] Subjects should start therapy within 72 hours of randomization.
[bb] Echocardiogram to be performed as clinically indicated..

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 2686-2689.

Table 12 Pharmacokinetic Sampling Schedule

Cycle 1			
Day 11	**Day 12**	**Day 13**	**Day 14**
0 minutes pre-dose	24 hours, 32 hours post-dose	48 hours post-dose	72 hours post -dose
2 minutes post-dose			
5 minutes post-dose			
15 minutes post-dose			
30 minutes post–dose			
1 hour post-dose			
2 hours post-dose			
4 hours post-dose			
6 hours post-dose			
10 hours post-dose			

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 2690.

Stopping Criteria

Treatment would be discontinued if:

- The investigator believed that, for safety reasons (i.e., adverse event), it was in the best interest of the subject to stop treatment
- The subject became pregnant
- The subject had unacceptable toxicity after 2 dose reductions of Velcade (to 0.7 mg/m^2), in which case all study drug treatment was to be discontinued. If the toxicity was related to dexamethasone alone, treatment with Velcade could continue and only treatment with dexamethasone was to be discontinued
- The recovery of toxicity to a level allowing the start of a new cycle had not occurred within the 2-week window
- Disease progression occurred
- The subject declined further treatment

6 Review of Efficacy

Efficacy Summary

The new, subcutaneous, route of administration of Velcade was non-inferior in efficacy to the approved IV route of administration. The pivotal randomized open-label phase 3 trial, MMY-3021, in support of the subcutaneous route of administration has met the non-inferiority objective for the primary efficacy endpoint of overall response rate (complete response + partial response).

The pivotal clinical trial (MMY-3021) met the primary objective of non-inferiority for the primary efficacy endpoint of ORR (CR+PR) after 4 cycles of Velcade for both SC and IV routes. The ORR was 43% in the SC and 42% in the IV treatment group using the intent-to-treat (ITT) population (with a 95% CI for the difference in ORR-SC-0.6 ORR_IV of 7.0, 27.9).The response rate of the patients in the IV arm (42%) in this trial was consistent with the previous single agent IV Velcade administration trials (41% in APEX and 38% in DOXIL-MMY-3001).

6.1 Indication

The sponsor is seeking approval for a new, subcutaneous route of administration of the previously approved drug Velcade (bortezomib) for the same approved indications.

6.1.1 Methods

A single randomized trial was provided for review, therefore no pooled clinical efficacy analysis was conducted by FDA.

This was a randomized open label trial. There were no significant problems with the design. Since the primary endpoint was response rate, which can be evaluated rather objectively, a blinded trial was not needed. A blinded trial would have been difficult given the two different routes of administration.

For non-inferiority, the lower bound of the CI is to be ≥ 0. The CI and p-value calculation were based on normal approximation. The primary efficacy analysis of the ORR after 4 cycles of Velcade was presented for the ITT population. Overall type I error was controlled at 0.05. Comparisons of all secondary endpoints were exploratory.

6.1.2 Demographics

A total of 222 subjects with relapsed/refractory multiple myeloma who had received 1-3 prior lines of therapy (but who had not received Velcade previously) were enrolled and randomized 2:1 to SC and IV treatment groups (148 in the SC arm and 74 in the IV

arm), in Western Europe(33%), Eastern Europe(59%), Argentina (6%) and India (3%). **Error! Reference source not found.** summarizes subject enrollment by region.

Table 13 Subject Enrollment by Region and Country

Region Country	IV (N=74) n (%)	SC (N=148) n (%)	Total (N=222) n (%)
Western Europe	30 (41)	43 (29)	73 (33)
France	14 (19)	22 (15)	36 (16)
Belgium	5 (7)	7 (5)	12 (5)
Netherlands	4 (5)	6 (4)	10 (5)
Great Britain	3 (4)	6 (4)	9 (4)
Germany	4 (5)	2 (1)	6 (3)
Eastern Europe	33 (45)	97 (66)	130 (59)
Ukraine	17 (23)	51 (34)	68 (31)
Russia	9 (12)	26 (18)	35 (16)
Poland	7 (9)	20 (14)	27 (12)
Non-Europe	11 (15)	8 (5)	19 (9)
Argentina	8 (11)	5 (3)	13 (6)
India	3 (4)	3 (2)	6 (3)

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 71.

Demographics are presented in Table 14 below. The baseline demographic characteristics were well-balanced between the two treatment arms. Subjects were mostly white in both IV (96%) and SC (97%) arms. The median age was 64.5 years in both arms with 50% < 65 years and 50% ≥65 years in both the IV and SC treatment groups. There were more males (64%) in the IV group than females.

Subjects in the IV arm had higher mean Karnofsky Performance Status score (90%) than in SC (80%) group with 51% of subjects in IV group having a score of 90% or above compared to 40% of subjects in the SC group having score of 90% or above. This imbalance favored the IV arm.

Table 14 Demographics

	SC n=148 (%)	**IV n=74 (%)**
Age Mean Median	 64.3 64.5	 64.0 64.5
Gender Male Female	 74 (50) 74 (50)	 47 (64) 27 (36)

	SC n=148 (%)	**IV n=74 (%)**
Race		
White	143 (97)	71 (96)
Asian	5 (3)	3 (4)
Baseline KPS		
70	32 (22)	12 (16)
80	57 (39)	24 (32)
≥90	59 (40)	38 (51)
Mean	82.5	84.6
Median	80.0	90.0

Baseline disease characteristics were similar between the two treatment groups. Differences were noted in a few areas. For example, there were more subjects with IgG multiple myeloma in the IV group (72% versus 65%) and more subjects with IgA and IgD in the SC group compared to the IV group (26% versus 19%, and 1% versus 0, respectively). The mean IgG m-protein level was higher in the SC group than in the IV group (3.45 g/dL versus 3.07 g/dL) The mean IgA m-protein level was also higher in the SC group than in the IV group (2.65 g/dL versus 2.34 g/dL). Mean urine m-protein was also higher in the SC group than in the IV group (348.50 mg/24hr versus 195.94 mg/24hr).

Table 15 below summarizes the baseline disease characteristics. Such imbalance would be expected to adversely affect the data for SC Velcade administration, as there were more subjects with multiple myeloma characteristics that would tend to more adversely affect response to treatment.

Table 15 Baseline Myeloma Disease Characteristics

	-------- IV ------- (N=74)	-------- SC ------- (N=148)	------ Total ------ (N=222)
Measurable type as per central lab, n (%)			
N	74	148	222
Secretory	71 (96)	144 (97)	215 (97)
Oligosecretory	3 (4)	4 (3)	7 (3)
Specific myeloma type, n (%)			
N	74	148	222
IgG	53 (72)	96 (65)	149 (67)
- IgG, kappa	40 (54)	64 (43)	104 (47)
- IgG, lambda	13 (18)	32 (22)	45 (20)
IgA	14 (19)	38 (26)	52 (23)
- IgA, kappa	11 (15)	19 (13)	30 (14)
- IgA, lambda	3 (4)	19 (13)	22 (10)
IgD	0	1 (1)	1 (<1)
- IgD, lambda	0	1 (1)	1 (<1)
IgM	1 (1)	1 (1)	2 (1)
- IgM, kappa	1 (1)	1 (1)	2 (1)
Light chain	6 (8)	12 (8)	18 (8)
- kappa	3 (4)	8 (5)	11 (5)
- lambda	3 (4)	4 (3)	7 (3)
ISS staging[a], n (%)			
N	74	148	222
I	20 (27)	40 (27)	60 (27)
II	30 (41)	60 (41)	90 (41)
III	24 (32)	48 (32)	72 (32)
IgG (g/dL) m-protein			
N	53	96	149
Mean (SD)	3.07 (1.839)	3.45 (2.263)	3.32 (2.123)
Median	2.70	2.80	2.80
Range	(0.4;8.5)	(0.0;10.7)	(0.0;10.7)
IgA (g/dL) m-protein			
N	14	38	52
Mean (SD)	2.34 (1.282)	2.65 (1.890)	2.57 (1.740)
Median	2.05	2.35	2.25
Range	(0.9;5.3)	(0.0;8.4)	(0.0;8.4)
Urine m-protein (mg/24hr)			
N	74	148	222
Mean (SD)	195.94 (481.543)	348.50 (1017.710)	297.65 (877.906)
Median	0.00	0.00	0.00
Range	(0.0;2508.1)	(0.0;10310)	(0.0;10310)

Type of measurable myeloma and specific type are derived based on central lab data.
[a] ISS Staging is derived from baseline central laboratory data.
Urine m-protein is summarized for all subjects with available values.

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 76.

Subjects were stratified by disease stage and lines of prior therapy and thus were evenly distributed between the two treatment arms as summarized in Table 16 below.

Table 16 Baseline Disease Stage and Lines of Prior Therapy

	SC N=148 (%)	**IV** n=74 (%)
Lines of therapy		
1	92 (62)	48 (65)
2	36 (24)	17 (23)
3	20 (14)	9 (12)
International Staging System		
I	40 (27)	20 (27)
II	60 (41)	30 (41)
III	48 (32)	24 (32)

Other relevant baseline disease characteristics included years from diagnosis, cytogenetic risk status and bone marrow cell plasma percentage, as summarized in Table 17 below.

Table 17 Baseline Disease Characteristics

	SC n (%)	**IV n (%)**
Years from diagnosis	n=148	n=74
<1	36 (24)	15 (20)
>2	86 (58)	49 (66)
High risk cytogenetics	n=137 19 (14)	n= 69 13 (19)
% plasma cells bone marrow	n=148	n=73
<10%	26 (18)	16 (22)
10-30%	49 (33)	31 (42)
>30%	73 (49)	26 (36)

The number of lytic lesions and extramedullary plasmacytomas were similar for SC and IV groups with the exception that no patients in the IV group had had ≥3 plasmacytomas while 4 (3%) patients in SC had ≥3 extramedullary plasmacytomas.

Basline extent of disease is summarized in Table 18 below.

Table 18 Baseline Extent of Disease

	------- IV ------ (N=74)	------- SC ------ (N=148)	----- Total ----- (N=222)
Years from diagnosis			
N	74	148	222
Category, n (%)			
<1 year	15 (20)	36 (24)	51 (23)
1-2 years	10 (14)	26 (18)	36 (16)
>2 years	49 (66)	86 (58)	135 (61)
Mean (SD)	3.32 (2.477)	3.35 (3.213)	3.34 (2.982)
Median	2.93	2.68	2.77
Range	(0.2;13.4)	(0.2;20.7)	(0.2;20.7)
Number of lytic bone lesions, n (%)			
N	74	148	222
None	16 (22)	25 (17)	41 (18)
1-3	12 (16)	24 (16)	36 (16)
4-10	11 (15)	30 (20)	41 (18)
More than 10	34 (46)	69 (47)	103 (46)
Missing	1 (1)	0	1 (<1)
Number of extramedullary plasmacytomas, n (%)			
N	74	148	222
0	70 (95)	136 (92)	206 (93)
1	3 (4)	8 (5)	11 (5)
2	1 (1)	0	1 (<1)
≥3	0	4 (3)	4 (2)
% plasma cells[a]			
N	73	148	221
Category, n (%)			
<10	16 (22)	26 (18)	42 (19)
10-30	31 (42)	49 (33)	80 (36)
>30	26 (36)	73 (49)	99 (45)
Mean (SD)	30.78 (24.729)	34.13 (26.515)	33.03 (25.930)
Median	22.50	30.00	27.00
Range	(0.4;90.0)	(0.0;100.0)	(0.0;100.0)
Cytogenetic abnormality category, n (%)			
N	69	137	206
Standard risk	56 (81)	118 (86)	174 (84)
High risk	13 (19)	19 (14)	32 (16)

Note: High risk for cytogenetic abnormality consists of the following criteria: Deletion 17p by FISH or karyotype, T(4;14) by FISH or karyotype, T(14;16) by FISH, Deletion 13 by karyotype, Hypoploidy by karyotype.
[a] Based on combined results from bone marrow aspirate and biopsy.

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 78.

Baseline hematologic values were well balanced between the SC and IV groups, and are summarized in Table 19 below. Several subjects in the SC group had grade ≥3 anemia and neutropenia (3% and 1%, respectively) while no subjects in the IV group had baseline high grade anemia or neutropenia.

Table 19 Baseline Hematological Characteristics

	SC n=148	**IV n=74**
Anemia Grade ≥3	4 (3%)	0
Neutropenia Grade ≥3	2 (1%)	0
Median Hct %	32.0% (19.7;46.0)	32.8% (23.9;47.0)
Median Platelet Count	207.0 (50;571)	207.5 (55;433)
Median WBC Count	5.01 (2.1;14.1)	4.85 (2.3;11.2)

Disease related pertinent laboratory parameters were similar between the two groups and are summarized in Table 20 below. More subjects in the IV group had higher creatinine clearance (68% versus 59%).

Table 20 Baseline Disease Related Laboratory Parameters

	SC n=148 (%)	IV n=74 (%)
B2 microglobulin (mg/L)		
<3.5	49 (33)	26 (35)
≥5.5	48 (32)	24 (32)
Albumin (g/dL)		
<3.5	70 (47)	32 (43)
Creatinine Clearance (mL/min)		
>20-30	5 (3)	2 (3)
>30-60	55 (37)	22 (30)
>60	88 (59)	50 (68)
Median B2 microglobulin	4.2 (1.7;38.4)	4.25 (1.6;19.4)
Median Albumin	3.55 (2.0;4.6)	3.60 (2.1;4.6)
Median Creatinine Clearance	67.5 (23;144)	73.0 (28;150)

Other baseline conditions of interest which are known potential toxicities associated with Velcade, including neuropathies and cardiac disease, were similar at baseline between the two groups with the exception that more subjects had a baseline history of sensory neuropathy in the IV group and more subjects had a baseline history of cardiac disease in the SC group, as summarized in Table 21 below.

Table 21 Selected Baseline Medical History

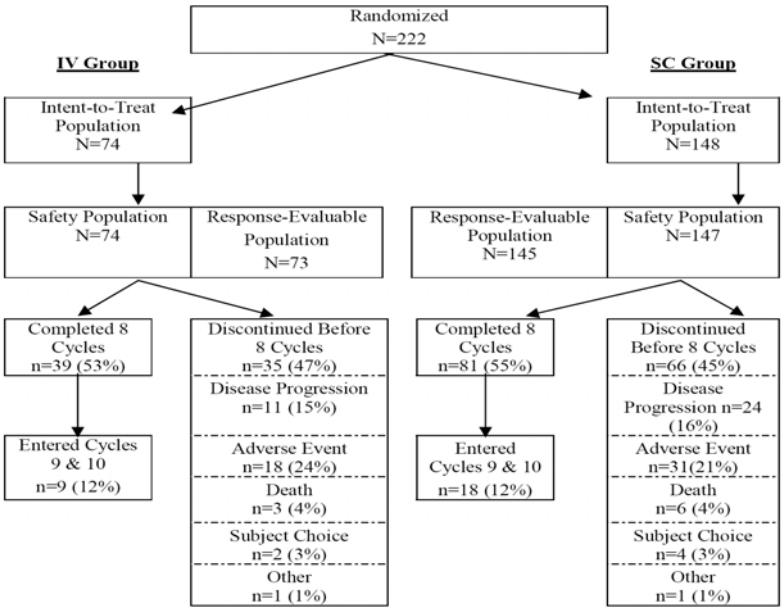
	SC n=148	**IV n=74**
Baseline history of sensory neuropathy	31 (21)	20 (**27**)
Baseline history of motor neuropathy	3 (2)	1 (1)
Baseline history of cardiac disease	41 (**28**)	17 (23)
Abnormal clinically significant EKG at baseline	2 (1)	0

Reviewer comment: *For the most part, demographics, baseline characteristics, including disease characteristics and other clinical parameters, were similar and well-balanced between the treatment groups. When imbalanced, however, the baseline parameters tended to be less favorable for the SC group (greater number of subjects with worse disease characteristics in the SC group than the IV group), potentially negatively impacting efficacy and safety of the SC group compared to IV. However, despite these imbalances in favor of the IV route of administration, the data indicate that SC route is not less effective as evidenced by the trial meeting its the non-inferiority objective.*

6.1.3 Subject Disposition

Of the 148 subjects randomized to the SC arm, 1 subject was randomized but did not receive study medication due to progression of disease prior to the start of the trial. This subject was excluded from the safety and response evaluable population analyses by the Applicant. The response-evaluation population consisted of all subjects who received at least one dose of study medication and had measurable disease at study entry, which was 145 subjects in the SC arm and 73 subjects in the IV arm (for a total of 218 subjects). The safety population consisted of all subjects randomized who received at least one dose of study drug; 147 subjects in the SC arm and 74 subjects in the IV arm (for a total of 221 subjects). The intent to treat population (ITT) consisted of all subjects randomized (148 in the SC arm and 74 in the IV arm). The FDA used the intent to treat population (ITT) for efficacy analyses and the safety population for safety analyses. Figure 5 and Table 22 below summarize subject disposition.

Figure 5: Subject Disposition



Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 74.

Table 22: Subject Disposition

Treatment Status Reason for Treatment Termination	IV (N=74) n (%)	SC (N=148) n (%)	Total (N=222) n (%)
Not treated	0	1 (1)	1 (<1)
Treated	74 (100)	147 (99)	221 (>99)
Cycles 1-8	74 (100)	147 (99)	221 (>99)
Protocol completed	50 (68)	105 (71)	155 (70)
Treatment completed	39 (53)	81 (55)	120 (54)
Treatment discontinued due to pd	11 (15)	24 (16)	35 (16)
Treatment discontinued	24 (32)	42 (28)	66 (30)
Subject choice	2 (3)	4 (3)	6 (3)
Adverse event	18 (24)	31 (21)	49 (22)
--related adverse event	15 (20)	24 (16)	39 (18)
--unrelated adverse event	3 (4)	7 (5)	10 (5)
Death	3 (4)	6 (4)	9 (4)
Other	1 (1)	1 (1)	2 (1)
Cycles 9-10	9 (12)	18 (12)	27 (12)
Protocol completed	7 (9)	14 (9)	21 (9)
Treatment completed	7 (9)	14 (9)	21 (9)
Treatment ongoing[a]	0	2 (1)	2 (1)
Treatment discontinued	2 (3)	2 (1)	4 (2)
Adverse event	2 (3)	2 (1)	4 (2)
--related adverse event	2 (3)	2 (1)	4 (2)
Enrolled in PK substudy	14 (19)	18 (12)	32 (14)

Note: Percentages calculated with the number of subjects in each group as denominator.

[a] At the time of the clinical cutoff, two subjects had not yet completed the end of extension treatment visit with one patient having to complete his final dose of VELCADE.

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 73.

Of the 147 subjects in the SC treatment group who received at least one dose of subcutaneous Velcade, 81 subjects (55%) completed 8 cycles of treatment, 24 subjects (16%) discontinued due to disease progression, and 42 subjects (28%) discontinued for reasons other than disease progression. Of the 74 subjects who received at least one dose of intravenous Velcade, 50 subjects (68%) completed 8 cycles of treatment, 11 (15%) discontinued due to disease progression, and 24 (32%) discontinued for reasons other than disease progression.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint of this trial was overall response rate (ORR) after 4 cycles of Velcade, with the intent to demonstrate non-inferiority of SC compared to IV bortezomib for the primary endpoint, with non-inferiority defined as retention of 60% of the IV (active) treatment effect (as measured by ORR).

Reviewer comment: The endpoint was acceptable as it is clinically relevant and has been previously used for regulatory action in multiple myeloma approvals.

The FDA used the intent to treat population (ITT) of 148 subjects in the SC and 74 subjects in the IV arm for efficacy analyses. The applicant used the response evaluable population data for efficacy analysis. Per the applicant's analysis, SC response rate for the primary endpoint of ORR after the first 4 cycles was 42% and IV response rate was 42%; using the ITT population, the SC response rate was 43% and the IV response rate was 42%. For additional details, see the statistical review for this NDA supplement. The subject who did not receive a dose of Velcade (randomized to SC group but did not receive any Velcade as the subject's condition deteriorated prior to study initiation) was removed from the ITT. This did not significantly impact the results as evident from the analysis using intent to treat versus response evaluable population.

The response rate of the IV route of administration (42%) was similar to the rate in the 2005 Velcade approval for use in multiple myeloma patients with at least one line of prior therapy (38%).

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints included complete response (CR), near complete response (nCR), and very good partial response (VGPR) rates after 4 cycles of single-agent Velcade, overall response rate (ORR) after 8 cycles of treatment (including effect of addition of dexamethasone), duration of response, time to progression (TTP), progression-free survival (PFS), 1-year survival, and time to response. Using the ITT population data, FDA analysis was consistent with the applicant's analysis. The applicant used data from the response evaluable population as summarized in the Table 23 below. FDA analysis using ITT population is shown in Table 24.

The CR rate after 4 cycles of treatment was 6% in the SC treatment group and 8% in the IV treatment group; the nCR rate after 4 cycles of treatment was 6% in the SC treatment group and 5% in the IV treatment group; the VGPR rate after 4 cycles of treatment was 4% in the SC treatment group and 3% in the IV treatment group.

The ORR (CR+PR) after 8 cycles of treatment was 52% in both the SC and IV treatment groups for the response-evaluable population.

The median TTP was 10.4 months in the SC treatment group and 9.4 months in the IV treatment group. The hazard ratio was 0.839 with 95% CI of (0.564, 1.249), and the p-value was 0.386, similar between the treatment groups.
The median PFS was 10.2 month in the SC treatment group and 8.0 months in the IV treatment group. The hazard ratio was 0.824 with 95% CI of (0.57, 1.18), and p-value was 0.29, indicating comparable results between the two treatment groups.

The 1-year survival rate was 72.6% in the SC treatment and 76.7% in the IV arm. The p-value for the difference in 1-year survival rate was 0.5.

Table 23: Best Response During First 4 Cycles – Response Evaluable Population

Best Response[a]	--- IV --- - N (%) -	--- SC --- - N (%) -	--- Rate Difference -- 95% CI[b]	-- Relative Risk[c] - 95% CI	P-value[d]
Total no. subjects	73	145			
Complete response (CR)	6 (8)	9 (6)	-2.0 (-9.4 , 5.4)		
Partial response (PR)	25 (34)	52 (36)	1.6 (-11.8 , 15.0)		
- near CR	4 (5)	9 (6)	0.7 (-5.8 , 7.3)		
- very good PR	2 (3)	6 (4)	1.4 (-3.6 , 6.4)		
At least very good PR	12 (16)	24 (17)	0.1 (-10.3 , 10.5)		
Overall response rate (CR, PR)	31 (42)	61 (42)	-0.4 (-14.3 , 13.5)	0.99 (0.71,1.37)	0.00201
Minor response (MR)	10 (14)	20 (14)	0.1 (-9.6 , 9.8)		
Overall response + MR	41 (56)	81 (56)	-0.3 (-14.3 , 13.7)	0.99 (0.77,1.26)	0.00004
No change	25 (34)	49 (34)			
Progressive disease	5 (7)	9 (6)			
Not evaluable	2 (3)	6 (4)			

Note: Very Good PR is a subcategory of PR where subjects meet the following criteria:
Heavy chain subjects: At least 90% reduction in serum m-protein and urine m-protein <100 mg/24hr.
Light chain subjects: Non-measurable serum m-protein and urine m-protein <100 mg/24hr.
Note: Near CR is a subcategory of PR where subjects meet the following criteria:
Positive immunofixation analysis of serum or urine as the only evidence of disease.
Disappearance of any soft tissue plasmacytomas.
Note: At Least VGPR includes categories of Very Good PR, Near CR, and Complete Response.
[a] Based on programmed algorithm.
[b] 95% CI for SC rate - IV rate is based on normal approximation
[c] Stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV is used.
[d] P-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in IV.

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 105.

Table 24: FDA Analysis of Best Response – ITT Population

Best Response	**SC (N=148)**	**IV (N=74)**	**Rate Diff (95% CI)**	**Relative Risk (95% CI)**
CR	11 (7%)	6 (8%)	-0.7% (-8.2, 6.8)	
PR	52 (35%)	25 (34%)	1.4% (-11.9, 14.6)	
MR	20 (14%)	10 (14%)	0.0 (-9.5, 9.5)	

Overall Resp+MR	83 (56%)	41 (55%)	0.7% (-13.2, 14.5)	1.01 (0.79, 1.29)
PD	9 (6%)	5 (7%)		
nCR	9 (6%)	4 (5%)	0.7% (-5.8, 7.1)	
VGPR	6 (4%)	2 (3%)	1.4% (-3.5, 6.2)	

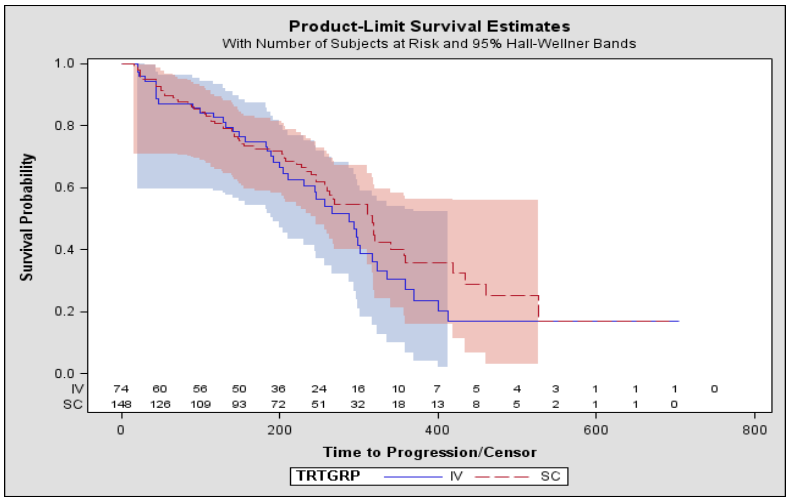
Source: FDA analysis

Response rates for the secondary endpoints were comparable for the two treatment groups. After the first 4 cycles 11 of subjects (7%) in the SC treatment group had CR, compared to 6 subjects (8%) in the IV treatment group; 20 subjects (14%) in the SC treatment group had MR, compared to 10 subjects (14%) in IV treatment group; 52 subjects (35%) in the SC treatment group had PR, compared to 25 subjects (34%) in the IV treatment group. The overall response rate after 8 cycles was comparable in the two treatment groups using ITT population with 53% response rate in the SC and 51% response rate in the IV group (P-value was <0.0001); this was similar to the response rate of 52% in both groups, using response evaluable population data. For the secondary endpoint of time to progression, defined as days between date of randomization and date of first documented evidence of disease progression, using ITT population data, and censored for subsequent therapy, there was a median of 64 events (43.2%) in the SC arm and 41 events (55.4%) in the IV arm. Median progression free survival was 10.2 months in the SC group and 8.0 months in the IV group, with a hazard ratio of 0.839 (SC versus IV).

Efficacy result differences between FDA and applicant analysis relates to use of response evaluable population by the applicant and ITT by the FDA. However, the results using response evaluable versus ITT population are comparable.

The Kaplan-Meier plot of time to disease progression below in Figure 6 is based on FDA's analysis using the ITT population.

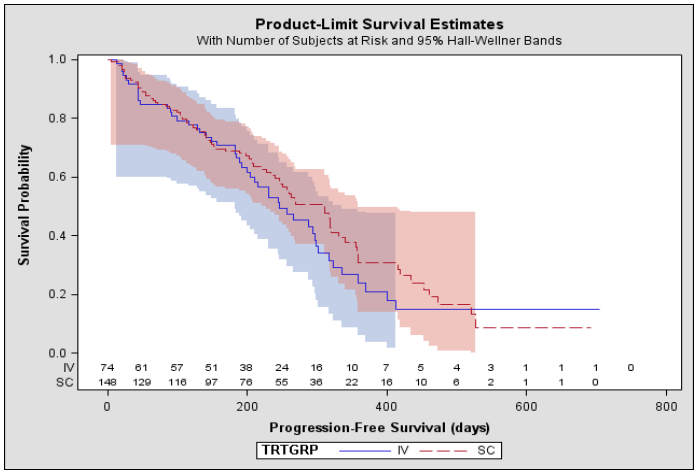
Figure 6: Kaplan-Meier Plot Time to Disease Progression – ITT Population



Source: FDA analysis

The Kaplan-Meier plot of progression free survival below in Figure 7 is based on FDA's analysis using the ITT population. The results were not statistically significant.

Figure 7: Kaplan-Meier Plot of Progression Free Survival – ITT Population

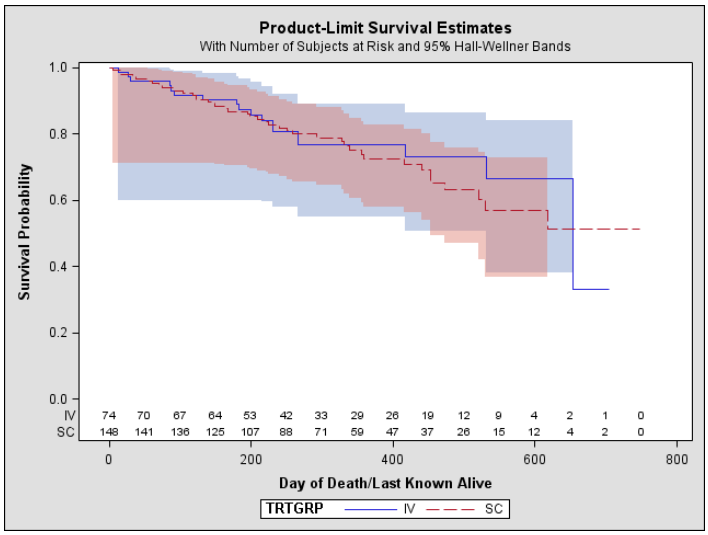


Source: FDA analysis

Median PFS was 8.8 months in SC and 8.0 months in IV (HR 0.832, 95% CI 0.582, 1.189, P-value 0.31125). The results were not statistically significant.

The Kaplan-Meier plot of overall survival in Figure 8 is based on FDA's analysis using the ITT population.

Figure 8: Kaplan-Meier Plot of Overall Survival – ITT Population



Source: FDA analysis

Median overall survival was 654 days in the IV arm and not estimable in the SC arm with 95% CI (654.0; NE). No formal conclusion about median overall survival could therefore be drawn.

There were 41 events (27.7%) in the SC group and 18 events (24.3%) in the IV group, with a 1-year survival rate of 72.6 in the SC and 76.7% in the IV group (P-value 0.5, which indicates no statistically significant difference in 1-year survival).

6.1.6 Other Endpoints

Eighteen subjects from the SC group and 14 subjects from the IV group participated in the pharmacokinetic/pharmacodynamic subgroup, of which 17 subjects in the SC group and all 14 subjects in the IV group provided samples for PK and PD analysis. Per the applicant's analysis, peak bortezomib concentrations were higher following IV administration. The mean percent inhibition of proteosome activity (E_{max}) was comparable for the SC and IV treatment groups. As for the rotation of SC injection sites (left and right abdomen and left and right thigh), there was no difference in bortezomib systemic exposure related to site of injection. The results of the applicant's analysis of the exploratory PK/PD subgroup evaluation in this phase III trial (MMY-3021) are consistent with those of the phase I PK/PD trial (CAN-1004). For additional detail, please see the Clinical Pharmacology review.

6.1.7 Subpopulations

The subjects were stratified by number of lines of prior therapy (1 versus > 1) and ISS staging (I, II, and III). Additional pertinent subgroup analyses included gender, age, and geographic region. The tables below summarized FDA analysis by subgroups using response-evaluable population data for ORR for the first 4 cycles (primary endpoint).

Table 25: Subgroup Analysis By Prior Lines of Therapy – Response-Evaluable Population

Number of Prior Lines of Therapy:1				
	SC (N=88)	IV (N=48)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	40 (45%)	21 (44%)	1.7 (-15.8, 19.2)	1.04 (0.71, 1.54)
Number of Prior Lines of Therapy:>1				
	SC (N=57)	IV (N=25)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	21 (37%)	10 (40%)	-3.2 (-26.1, 19.8)	0.87 (0.46, 1.62)

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV
Source: FDA analysis

Table 26: Subgroup Analysis By ISS Staging – Response-Evaluable Population

Staging I				
	SC (N=38)	IV (N=20)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	18 (47%)	7 (35%)	12.4 (-13.9, 38.6)	1.35 (0.69, 2.64)
Staging II				
	SC (N=60)	IV (N=29)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	29 (48%)	14 (48%)	0.1 (-22.1, 22.2)	0.95 (0.60, 1.50)
Staging III				
	SC (N=47)	IV (N=24)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	14 (30%)	10 (42%)	-11.9 (-35.5, 11.8)	0.77 (0.38, 1.54)

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV
Source: FDA analysis

The tables below summarize best confirmed response for the first 4 cycles in the subgroups analyzed.

Table 27: Subgroup Analysis: Eastern Europe – Response-Evaluable Population

Response	SC (N=96)	IV (N=23)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	39 (41%)	12 (36%)	4.3 (-14.9, 23.4)	1.13 (0.67, 1.89)
CR	7 (7%)	3 (9%)	-1.8 (-12.9, 9.3)	
PR	32 (33%)	9 (27%)	6.1 (-11.8, 23.9)	
MR	13 (14%)	7 (21%)	-7.7 (-23.2, 7.9)	
ORR+MR	52 (54%)	19 (58%)	-3.4 (-23.0, 16.2)	0.93 (0.67, 1.30)
nCR	6 (6%)	1 (3%)	3.2 (-4.4, 10.8)	
VGPR	3 (3%)	1 (3%)	0.1 (-6.7, 6.9)	
PD	5 (5%)	3 (9%)		

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV
Source: FDA analysis

Table 28: Subgroup Analysis: Western Europe – Response-Evaluable Population

Response	SC (N=41)	IV (N=30)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	21 (51%)	15 (50%)	1.2 (-22.3, 24.8)	1.05 (0.66, 1.66)
CR	2 (5%)	2 (7%)	-1.8 (-12.9, 9.3)	
PR	19 (46%)	13 (43%)	3.0 (-20.4, 26.4)	
MR	6 (15%)	1 (3%)	11.3 (-1.3, 23.9)	
ORR+MR	27 (66%)	16 (53%)	12.5 (10.5, 35.5)	1.24 (0.83, 1.86)
nCR	2 (5%)	2 (7%)	-1.8 (-12.9, 9.3)	
VGPR	3 (7%)	1 (3%)	4.0 (-1.6, 14.2)	
PD	3 (7%)	1 (3%)		

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV
Source: FDA analysis

Table 29: Subgroup Analysis: Non-Europe (Argentina and India) – Response-Evaluable Population

Response	IV (N=10)	SC (N=8)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	4 (40%)	1 (13%)	-27.5 (-65.5, 10.5)	0.69 (0.08, 6.11)
CR	1 (10%)	0	-10.0 (-28.6, 8.6)	
PR	3 (30%)	1 (13%)	-17.5 (-54.0, 19.0)	
MR	2 (20%)	1 (13%)	-7.5 (-41.3, 26.3)	
ORR+MR	6 (60%)	2 (25%)	-35.0 (-77.7, 7.7)	0.48 (0.11, 2.03)
nCR	1 (10%)	1 (13%)	2.5 (-27.0, 32.0)	
VGPR	0	0	0	
PD	1 (10%)	1 (13%)		

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV
Source: FDA analysis

Table 30: Subgroup Analysis for Primary Efficacy Endpoint

Subgroup	RR (95% CI)	Lower 95% CI (SC-0.6IV)	IV Resp/N	SC Resp/N
Age <65	0.76 (0.44, 1.17)	-0.07	16/36	25/74
Non-Europe	0.69 (0.08, 6.11)	-0.41	4/10	1/8
# of Prior Lines>1	0.86 (0.44, 1.67)	-0.04	10/25	20/55
ISS stage III	0.77 (0.38, 1.54)	-0.12	10/24	14/47
Prior transplantation exposure (Y)	0.85 (0.49, 1.47)	-0.108	12/20	15/30
Prior thalidomide exposure (Y)	0.70 (0.41, 1.19)	-0.10	16/34	19/55
Prior IMID Exposure	0.81 (0.48, 1.36)	-0.05	16/38	21/60

Source: FDA analysis

Reviewer comment: *The subgroup analyses do not suggest any clinically significant differences among groups, although, the lower bounds of 95% non-inferiority CI from some of the subgroup analyses are below 0 and therefore do not meet the non-inferiority criterion as shown in Table 30 above. However those subgroup analyses are to be considered only exploratory and not conclusive as the study is not adequately powered to detect clinically statistically significant differences among subgroups.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing recommendation is adequate and appropriate for the proposed subcutaneous route of administration. The subcutaneous and intravenous routes of administration have comparable PK/PD profiles. For additional detail, please refer to clinical pharmacology review of the phase I PK/PD trial (CAN-1004) and the clinical pharmacology review of PK/PD portion of the phase III trial (MMY-3021).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Median time to response was 54.5 days for SC group (SD 77) with a 95% CI (74, 99) and median time to response was 47 days for IV group (SD 114) with a 95% CI

(75,128). Median duration of response for the SC group was 204 days (SD 119) with a 95% CI (208,261) and median duration of response for the IV group was -198 days (SD 118) with a 95% CI (189, 257). The median time to response was longer for the SC group than IV, however, median duration of response was comparable for the two groups.

Per the applicant's analysis in Table 31 below, using data from responders in response evaluable population, the median time to first response (time to response) was 44 days in the SC group and 43 days in the IV group.

Table 31: Applicant's analysis of time to response for responders in response evaluable population

	-------- IV ------- (N=38)	-------- SC ------- (N=76)
Time to first response (days)		
N	38	76
Mean (SD)	59.3 (43.40)	55.4 (38.12)
Median	43.0	44.0
Range	(21;162)	(20;180)
Time to best response (days)		
N	38	76
Mean (SD)	71.8 (48.62)	71.6 (51.20)
Median	46.0	49.5
Range	(22;192)	(21;278)
Time to complete response (days)		
N	9	17
Mean (SD)	77.4 (63.19)	107.9 (67.67)
Median	44.0	87.0
Range	(22;192)	(22;278)

Note: Time to complete response does not include the date of bone marrow assessment.

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 126.

Per the applicant's analysis in the Table 32 below, using data of responders from response evaluable population, the median response duration was 295 days in the SC group and 266 days in the IV group.

Table 32: Applicant's analysis of response duration for responders in response evaluable population

Descriptive[a]	IV (N=38)	SC (N=76)	Total (N=114)
Duration of response (days)			
Number of Assessed	38	76	114
Number of Censored (%)	20 (52.6)	45 (59.2)	65 (57.0)
Number of Events (%)	18 (47.4)	31 (40.8)	49 (43.0)
25% Quantile (95% CI)	204.0(162.0; 254.0)	184.0(144.0; 255.0)	197.0(164.0; 247.0)
Median (95% CI)	266.0(230.0; 369.0)	295.0(255.0; 464.0)	295.0(254.0; 391.0)
75% Quantile (95% CI)	369.0(294.0; NE)	464.0(399.0; NE)	464.0(391.0; NE)

NE=Not estimable.
[a] Based on Kaplan-Meier product limit estimates.

Source: Applicant submission Clinical Study Reports 26866138-MMY-3021 – *Module 5; 5.3.5.1.2– Report Body* page 127.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable to this review.

7 Review of Safety

Safety Summary

7.1 Methods

The safety analysis was conducted using the safety population data (147 subjects in the SC and 74 subjects in the IV treatment groups). The safety population consisted of all patients enrolled who received at least one dose of bortezomib.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The trial used to evaluate safety was MMY-3021, the pivotal phase 3 trial, previously described in sections 5 and 6, which compares the new proposed subcutaneous route of administration to the previously approved IV route.

7.1.2 Categorization of Adverse Events

Adverse events were categorized according to CTCAE (V 3.0) and MEDRA and were adequately coded.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data is not appropriate because this submission included one pivotal trial.

7.2 Adequacy of Safety Assessments

The safety assessments and monitoring were adequate. Please see Table 11 summarizing assessments and monitoring for trial MM-3021 in section 5 of this review. The trial involved two different routes of administration for the same drug.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The two treatment groups had comparable drug exposure. Table 33 below summarizes trial drug exposure.

Table 33 Trial Drug Exposure – Safety-Evaluable Population

	SC n=147	IV N=74
Median Exposure (weeks)	22.6 (0.1-33)	22.6 (0.6-30.7)
Median Number of Cycles	8 (1-10)	8 (1-10)
Median Dose Exposure per Cycle (mg/m^2) Cycles 1-4	5.13 (1.2-5.3)	4.89 (2.4-5.4)
Median Dose Exposure per Cycle (mg/m^2) Cycles ≥5	4.88 (1.3-5.3)	4.91 (1.4-5.5)

A total of 82 subjects (56%) in the SC group and 39 subjects (53%) in the IV group received dexamethasone after cycle 4. Exposure to Dexamethasone was equal in the two treatment groups (160mg/cycle).

7.2.2 Explorations for Dose Response

Not applicable for this submission because it is an efficacy supplement. Please see prior reviews.

7.2.3 Special Animal and/or In Vitro Testing

Local tolerability/tissue reaction potential of Velcade was evaluated in female New-Zealand White rabbits following a single subcutaneous injection at a dose of 0.1 mg/kg (1.2 mg/m^2) at two different concentrations 3.5 mg/mL and 1.0 mg/mL. Clinical observations for signs of toxicity or irritation at the injection sites were made daily. Necropsies were performed on all rabbits on study days 1 and 4. The injection sites and

surrounding tissues from each rabbit were dissected and examined macroscopically and histopathologically. No mortality or treatment related clinical observations or changes in body weight and weight gain were reported during the study.

Gross pathological signs seen at the bortezomib and vehicle injection sites were slight to marked subcutaneous hemorrhages in a few rabbits mainly related to the injection procedure. Edema noted at the bortezomib injection site of one rabbit dosed with bortezomib concentration of 3.5 mg/mL and sacrificed 3 days after injection was considered test article related. Minimal reaction in the bortezomib injection site in 4 out of 12 female rabbits that were subcutaneously injected with 0.1 mg JNJ-26866138/kg body weight at a concentration of 3.5 or 1.0 mg/mL and killed 1 or 3 days, respectively after injection was reported, based on histopathological examination. .

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate. See section 5.3 for discussion and summary of clinical testing conducted in the pivotal trial. Safety concerns with Velcade include neurotoxicity, cytopenias, cardiac, gastrointestinal, infectious, vascular, and injection site reactions (especially with subcutaneous injection)/adverse events. The sponsor adequately monitored for these during scheduled visits. The injection site was evaluated 2-4 hours after each SC injection and IV infusion during cycle 1 only and at investigator discretion subsequently. If there was evidence of injection site reaction, additional evaluations would be performed. The patients also were to keep a special diary to record time and location of the injection and the type, onset, severity, and resolution of any local injection site reactions/symptoms that persisted longer than 24 hours. Subjects were given diary cards that were to be brought to each visit.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable. Please see prior reviews.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Bortezomib is the only approved proteosome inhibitor.

7.3 Major Safety Results

The safety profile was comparable for the proposed new SC and previously approved IV routes of administration with 95% of subjects in the SC arm and 99% of subjects in the IV arm reporting at least 1 treatment-emergent AE. The SC treatment group had a lower incidence of: grade $\geq$3 adverse events (SC 57% versus IV 70%); adverse events leading to discontinuation (SC 22% versus IV 27%); adverse events leading to dose modification (dose reduction [SC 33% versus IV 45%]; dose withholding [SC 30%

versus IV 39%]; and dose delay [SC 20% vs. IV 34%]). FDA analysis was consistent with that of the applicant.

The most common adverse events included anemia, neutropenia, thrombocytopenia, neuralgia, diarrhea, nauseas, vomiting, herpes zoster, and asthenia. The Table 34 below summarizes the safety analysis for adverse events occurring in ≥10% of subjects.

Table 34 AE in ≥10% of Subjects - Safety-Evaluable Population

Adverse Event	SC All Grades (%) n= 147	IV All Grades (%) n=74	SC Grade 3-4 (%)	IV Grade 3-4 (%)
ANAEMIA	56 (37.8)	26 (35.1)	19 (12.8)	6 (8.11)
THROMBOCYTOPENIA	53 (35.8)	27 (36.5)	21 (14. 2)	14 (18.9)
PERIPHERAL SENSORY NEUROPATHY	52 (35.1)	36 (48.6)	7 (4.73)	11 (14.9)
NEUTROPENIA	42 (28.4)	20 (27)	26 (17.6)	13 (17.6)
DIARRHOEA	36 (24.3)	27 (36.5)	3 (2.03)	4 (5.41)
NEURALGIA	35 (23.6)	17 (23)	5 (3.38)	7 (9.46)
LEUKOPENIA	29 (19.6)	16 (21.6)	9 (6.08)	5 (6.76)
NAUSEA	28 (18.9)	14 (18.9)	0 (0)	0 (0)
PYREXIA	28 (18.9)	14 (18.9)	0 (0)	0 (0)
ASTHENIA	24 (16.2)	14 (18.9	4 (2.7)	4 (5.41)
WEIGHT DECREASED	22 (14.9)	3 (4.05)	0 (0)	1 (1.35)
BACK PAIN	21 (14.2)	8 (10.8)	1 (0.68)	2 (2.7)
CONSTIPATION	21 (14.2)	11 (14.9)	1 (0.68)	1 (1.35)
FATIGUE	18 (12.2)	16 (21.6)	3 (2.03)	3 (4.05)
INSOMNIA	18 (12.2)	8 (10.8)	0 (0)	0 (0)
HERPES ZOSTER	17 (11.5)	7 (9.46)	3 (2.03)	1 (1.35
VOMITING	17 (11.5)	12 (16.2)	3 (2.03)	1 (1.35)

7.3.1 Deaths

Deaths of all causes, any time during trial

Twenty-six per cent (26%) of subjects in the trial died (58/221). Of these, 24% (18/74) were in the IV arm and 27% (40/147) were in the SC arm. Table 35 below lists the number of deaths due to adverse events, disease progression and other causes.

Table 35 All Deaths During the Trial

Cause	**IV n=74 (%)**	**SC n = 147 (%)**
AE	7 (**9**)	5 (3)
PD	7 (9)	26 (**18**)
Other	4 (6)	9 (6)
Total	18 (24)	40 (27)

Of the 58 deaths, 13 (6%) were within 30 days of last trial drug dose. Of these, 5 (7%) occurred in the IV arm and 8 (5%) in the SC arm. Five of 13 deaths in the IV arm and 4 in the SC arm were due to AE; 1 of 5 in the IV arm and 2 of 4 in the SC arm were thought possible related to trial drug. No deaths in the IV group and 4 deaths in the SC group out of the 13 deaths within 30 days of last trial drug dose administration were due to disease progression. See Table 36 below.

Table 36: Deaths Within 30 Days of Drug Administration

	IV n=74 (%)	**SC n = 147 (%)**	**Total n= 221 (%)**
Number of deaths within 30 days post last dose of drug	5 (7)	8 (5)	13 (6)
Deaths due to AE within 30 days of last dose of drug	5 (7)	4 (3)	9 (4)
Deaths due to PD	0 (0)	4 (**3**)	4 (2)

Table 37 below summarizes the types of adverse events associated with death within 30 days of last drug dose administration.

Table 37 Types of AEs Associated With Deaths Within 30 Days of Drug Dose

Treatment arm	**Death due to AE – Type of AE**	**Days after last dose of drug**
SC	Acute cardiac failure	1
SC	Sudden death Reported as possibly related to trial drug	6
SC	Pneumonia Diarrhea	7
SC	Pneumonia Reported as possibly related to trial drug	30
IV	Cardiac arrest	3
IV	Myocardial infarction	3
IV	Coronary artery insufficiency Reported as possibly related to trial drug	5
IV	Multiorgan failure/brain edema	19
IV	Pneumonia	24

Three deaths were reported/assessed as possibly drug related:

1. 77-year old female in the SC arm died of pneumonia 29 days after drug was administered (cycle 1 day 36).
2. 61-year old male in the SC arm died suddenly (sudden death) 5 days after drug was

administered (cycle 1 day 16).
3. 83-year old male in the IV arm died of coronary artery insufficiency 4 days after drug was administered (cycle 4 day 15).

7.3.2 Nonfatal Serious Adverse Events

A total of 79 subjects experience SAEs; 53 (36%) in the SC arm and 26 (35%) in the IV arm. A total of 158 treatment emergent serious adverse events occurred; 105 in the IV arm and 53 in the SC arm. Trial drug was permanently discontinued in 17 (12%) of SC and 5 (6%) of IV treatment group subjects with serious adverse events.

The most frequently reported SAEs for the SC arm were pneumonia (6% in SC and 7% in IV), diarrhea (2 % in SC and 4% in IV), peripheral sensory neuropathy (1% in SC and 3% in IV), pyrexia (3% in SC and 0 in IV). Table 38 below lists the incidence of treatment emergent serious adverse events by system organ classification.

Table 38: Treatment Emergent SAEs

System Organ Classification	SC (%)	IV (%)
Blood and lymphatic system disorders	3 (2)	3 (4)
Cardiac disorders	8 (5)	5 (7)
Ear and labyrinth disorders	1 (1)	0 (0)
Gastrointestinal disorders	11 (6)	5 (7)
General disorders and administration site conditions	8 (9)	1 (1)
Hepatobiliary disorders	3 (2)	1 (1)
Infections and infestations	16 (11)	9 (12)
Injury, poisoning and procedural complications	2 (1)	1(1)
Metabolism and nutrition disorders	8 (5)	2 (3)
Musculoskeletal and connective tissue disorders	1 (1)	2 (3)
Neoplasms, benign, malignant and unspecified	1 (1)	2 (3)
Nervous system disorders	12 (8)	9 (12)
Psychiatric disorders	1 (1)	1 (1)
Renal and urinary disorders	6 (4)	3 (4)
Reproductive system and breast disorders	1 (1)	0 (0)
Respiratory, thoracic, and mediastinal disorders	9 (6)	5 (7)
Vascular disorders	3 (2)	2 (3)

Table 39: Treatment Emergent Serious Adverse Events of Differential Incidence >1%

System Organ Class *n (%)	**TE SAE Preferred Term**	**SC** Incidence (%)	**IV** Incidence (%)
Infections, Infestations SC 16 (11) IV 8(11)	Pneumonia	9 (6%)	5 (7%)
	† Herpes Zoster	2 (1%)	0
	† Injection site abscess	1 (1%)	0
Nervous System SC 10 (7) IV 4 (5)	Peripheral Sensory Neuropathy	2 (1%)	2 (3%)
	† Peripheral Motor Neuropathy	2 (1%)	1 (1%)
	† Peripheral Sensorimotor Neuropathy	1 (1%)	0
Gastrointestinal SC 8 (5) IV 4 (5)	Diarrhea	3 (2%)	3 (4%)
General/Admin Site SC 11 (7) IV 1 (1)	Pyrexia	4 (3%)	0
Renal and Urinary SC 7 (5) IV 3 (4)	Renal failure	3 (2%)	2 (3%)
Vascular SC 3 (2) IV 2 (3)	† Hypotension	0	1 (1%)
Metabolism and Nutrition SC 6(4) IV 2(3)	† Tumor lysis syndrome	2 (1%)	1 (1%)
Cardiac SC 7(5) IV 5(7)	† Atrial fibrillation	2 (1%)	0
	† Cardiac arrest	0	1 (1%)
	† Myocardial infarction	0	1 (1%)

* Total number (%) of patients who experienced Treatment Emergent SAE(s) per SOC
† SAEs of interest irrespective of differential occurrence or incidence

Lines of Therapy and Treatment Emergent Serious Adverse Events and Discontinuations

Subjects in both SC and IV treatment groups who had only 1 prior line of therapy had less SAEs (SC 32% versus IV 35%), grade ≥ 3 AEs (SC 51% versus IV 71%), and discontinuations due to AEs (SC 18% versus IV 23%) than those with >1 prior lines of therapy. For subjects with > 1 prior line of therapy, subjects in SC had higher rate of SAE's than IV subjects (SC 42% versus IV 35%). See Table 40 below.

Table 40: Prior Lines of Therapy and Treatment Emergent Serious AEs/Discontinuations

	SC			**IV**		
	Total n=147	**1 line** n=90	**>1 line** n=57	**Total** n=74	**1 line** n=48	**>1 line** n=26
TE SAE	53 (36%)	29 (32%)	24 (42%)	26 (35%)	17 (35%)	9 (35%)

Treatment D/C due to TE SAE	33 (22%)	16 (18%)	17 (30%)	20 (**27%**)	11 (23%)	9 (35%)

Reviewer Comment: Patients with more prior lines of therapy would be expected to experience more toxicity given exposure to an increased number and variety of drugs with adverse events particular to those drugs. Also, subjects with more lines of therapy are expected to be more ill and to have more complications from both the disease and its treatments.

7.3.3 Dropouts and/or Discontinuations

The most common treatment emergent serious adverse events leading to drug discontinuation were infections (pneumonia) and nervous system disorders (peripheral neuropathies). Adverse events led to discontinuation of 33 subjects (22%) in the SC and of 20 subjects (27%) in the IV arm. Peripheral neuropathy was the most common cause of discontinuation due to adverse events in both groups (12% in the SC and 15% in the IV group); peripheral sensory neuropathy was the most common of the peripheral neuropathies that led to discontinuation (5% in SC and 12% in the IV group).

7.3.4 Significant Adverse Events

Adverse events of interest include neurological, hematological, injection site, pulmonary, infections, cardiac, vascular, and tumor lysis categories. These adverse events and the incidence of these are listed in Table 41 below.

Table 41 Adverse Events of Interest

Adverse Event	SC all grade n (%)	SC Grade ≥ 3 n (%)	IV all grade n (%)	IV Grade ≥ 3 n (%)
Anemia	56 (37.8)	19 (12.8)	26 (35.1)	6 (8.1)
Thrombocytopenia	53 (35.8)	21 (14.2)	27 (36.5)	14 (18.9)
Peripheral sensory neuropathy	52 (35.1)	7 (4.7)	36 (48.6)	11 (14.9)
Neutropenia	42 (28.4)	26 (17.6)	20 (27)	13 (17.6)
Diarrhea	36 (24.3)	3 (2)	27 (36.5)	4 (5.4)
Vomiting	17 (11.5)	3 (2)	12 (16.2)	1 (1.4)
Herpes Zoster	17 (11.5)	3 (2)	7 (9.5)	1 (1.4)
Pneumonia	13 (8.8)	6 (4)	7 (9.5)	4 (5.4)
Peripheral motor neuropathy	7 (4.7)	1 (0.7)	3 (4)	2 (2.7)
Hypotension	6 (4)	0	4 (5.4)	1 (1.4)
Injection site erythema	5 (3.8)	1 (0.68)	0	0

Injection site pain/pruritus	2 (1.4)	0	0	0
Tumor lysis syndrome	2 (1.4)	2 (1.35)	1 (1.4)	1 (1.4)
Atrial fibrillation	2 (1.4)	1 (0.68)	1 (1.4)	0
Cardiac failure	2 (1.4)	1 (0.68)	1 (1.4)	0
Injection site reaction/induration	1 (0.7)	0	0	0
Myocardial infarction	1 (0.7)	0	1 (1.4)	0
Cardiac arrest	0	0	1 (1.4)	0

Neuropathy

Peripheral sensory neuropathy, all grades, was lower (35%) in the SC compared to IV (49%) treatment group as was grade ≥3 peripheral neuropathy (5% in the SC group compared to 15% in the IV group). Peripheral motor neuropathy all grades was similar in the two groups (5% in the SC and 4% in the IV group), while grade ≥3 peripheral motor neuropathy was lower in the SC group (0.68%) compared to the IV group (2.7%). More subjects in the IV group (27%) had baseline history of sensory neuropathy compared to the SC group (21%). Two percent of subjects in the SC and 1% in the IV treatment group had baseline history of motor neuropathy.

Hematological Toxicities

Anemia, all grades, was comparable in the SC (38 %) and IV (35%) treatment groups, while grade ≥3 anemia was slightly higher in the SC group (13%) than in the IV group (8%). Neutropenia, all grades, was comparable in both groups (28% in the SC group versus 27% in the IV group) and grade ≥3 neutropenia occurred at the same rate in both SC and IV treatment groups (18%). Thrombocytopenia, all grades, was comparable in both SC (36%) and IV (37%) groups, and grade ≥3 thrombocytopenia occurred at a slightly lower rate in the SC (14.2%) compared to the IV (19%) treatment group. Four subjects (4%) in the SC arm had grade ≥3 anemia and 2 subjects in the SC arm had ≥3 neutropenia at baseline as compared to no subjects with grade ≥3 anemia or grade ≥3 neutropenia in the IV arm.

Gastrointestinal Toxicities

Diarrhea, all grades, was lower in the SC arm (24%) compared to the IV arm (37%) as was grade ≥3 diarrhea slightly lower (2%) in the SC arm compared to the IV (5%) arm. There was a lower rate of vomiting in the SC group (12%) compared to the IV group (16%) and grade ≥3 vomiting was comparable for both groups (2% in the SC group versus 1% in the IV group).

Vascular

There was also a lower incidence of hypotension in the SC group with no grade ≥3 hypotension in the SC group compared to 1% in the IV group. All grades hypotension was similar between the two groups (4% in the SC group and 5% in the IV group).

Injection Site Reactions
The incidence of injection site reaction of erythema was higher in the SC group (3%; 0.68% grade ≥3) as compared to none in the IV group. Abcesses of all grades and grade ≥3 did not occur in the SC group while the incidence of abcess all grades and grade ≥3 was 2% in the IV group. Reaction and induration incidence, all grades, was 0.68% in the SC group and 0 in the IV group, with no grade ≥3 reaction or induration occurring in either group.

There were 9 (6%) of subjects with local reaction to SC administration of Velcade with the most common reaction being erythema in 6 of the 9 subjects and pruritis in 3 of the 9 subjects. Treatment consisted of local topical corticosteroids and oral systemic antihistamines for 4 of the 9 subjects; reduction of Velcade concentration from 2.5mg/mL to 1 mg/mL became necessary in 1 subject; treatment was discontinued in 1 subject.

Reviewer Comment: A higher number of injection site reactions is expected when transitioning to a subcutaneous route, with more local exposure of the drug to soft tissues.

Additional Adverse Events of Interest
There was a similar incidence (1%) of tumor lysis syndrome in both groups, all grades and grade ≥3. The incidence of cardiac adverse events was also low and similar, all grades and grade ≥3, in both groups.

7.3.5 Submission Specific Primary Safety Concerns

Velcade SC should not be self administered as the trial did not incorporate evaluation of self administration and the label does not provide for self administration.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events
Adverse events occurring in greater than 10% of subjects are listed in the order of frequency in Table 42 below.

Table 42: Common Adverse Events

Adverse Event	SC All Grades (%) n= 147	IV All Grades (%) n=74	SC Grade 3-4 (%)	IV Grade 3-4 (%)
ANAEMIA	56 (37.8)	26 (35.1)	19 (12.8)	6 (8.11)
THROMBOCYTOPENIA	53 (35.8)	27 (36.5)	21 (14. 2)	14 (18.9)

Adverse Event	SC All Grades (%) n= 147	IV All Grades (%) n=74	SC Grade 3-4 (%)	IV Grade 3-4 (%)
PERIPHERAL SENSORY NEUROPATHY	52 (35.1)	36 (48.6)	7 (4.73)	11 (14.9)
NEUTROPENIA	42 (28.4)	20 (27)	26 (17.6)	13 (17.6)
DIARRHOEA	36 (24.3)	27 (36.5)	3 (2.03)	4 (5.41)
NEURALGIA	35 (23.6)	17 (23)	5 (3.38)	7 (9.46)
LEUKOPENIA	29 (19.6)	16 (21.6)	9 (6.08)	5 (6.76)
NAUSEA	28 (18.9)	14 (18.9)	0 (0)	0 (0)
PYREXIA	28 (18.9)	14 (18.9)	0 (0)	0 (0)
ASTHENIA	24 (16.2)	14 (18.9	4 (2.7)	4 (5.41)
WEIGHT DECREASED	22 (14.9)	3 (4.05)	0 (0)	1 (1.35)
BACK PAIN	21 (14.2)	8 (10.8)	1 (0.68)	2 (2.7)
CONSTIPATION	21 (14.2)	11 (14.9)	1 (0.68)	1 (1.35)
FATIGUE	18 (12.2)	16 (21.6)	3 (2.03)	3 (4.05)
INSOMNIA	18 (12.2)	8 (10.8)	0 (0)	0 (0)
HERPES ZOSTER	17 (11.5)	7 (9.46)	3 (2.03)	1 (1.35
VOMITING	17 (11.5)	12 (16.2)	3 (2.03)	1 (1.35)

The most common adverse event reported in the SC arm (in ≥ 20% of subjects) were anemia (38%), thrombocytopenia (36%), neutropenia (28%), leukopenia (20%), peripheral sensory neuropathy (35%), neuralgia (24%), and diarrhea (24%). The most common adverse event reported in the IV arm (in ≥ 20% of subjects) were anemia (35%), thrombocytopenia (37%), neutropenia (27%), leukopenia (22%), peripheral sensory neuropathy (49%), neuralgia (23%), diarrhea (37%), and fatigue (20%). Peripheral sensory neuropathy occurred with lower incidence in the SC group (35% in SC vs. 49% in IV) as did diarrhea (24% in SC vs. 37% in IV) and fatigue (12% in SC vs. 22% in IV). There was a higher incidence of decreased weight in the SC group compared to the IV group (15% vs. 4%).

7.4.2 Laboratory Findings

The most common laboratory abnormalities in the SC group were hematological (anemia) in both groups as depicted in the Table 42 summarizing adverse events (38% in SC and 35% in IV). The baseline incidence of anemia grade >2 was higher in the SC group (31% in IV vs. 26% in IV). These laboratory abnormalities are expected as associated with Velcade and were similar in the two treatment groups.

7.4.3 Vital Signs

Weight loss was the most common vital sign abnormality in the two groups and occurred with a higher incidence in the SC group (15% in SC vs. 4% in IV) for all grades, but was similar for grade ≥ 3 for both groups (0 in SC and 1% in IV).

The incidence of hypertension (all grades) was 9.5% in the SC arm and 2% in the IV arm. The incidence of grade 3 and 4 hypertension was 4% in the SC and 0 in the IV arm. An evaluation of these cases revealed baseline hypertension in all three subjects, two of whom experienced the severe hypertension events while taking dexamethasone (after cycle 4). Thus, it does not appear that patients receiving SC Velcade were at increased risk of hypertension compared to patients in the IV group.

7.4.4 Electrocardiograms (ECGs)

The incidence of cardiac rate and rhythm disorders was similar in the two groups (3%) with 1% grade ≥ 3 rate and rhythm disorder in the SC group compared to 0 in the IV group.

Please refer to Section 4.4 for review of ECG data conducted by the FDA QT-IRT team from a Phase 1 trial.

7.4.5 Special Safety Studies/Clinical Trials

None found to be indicated in this review for this previously approved drug.

7.4.6 Immunogenicity

No new information found in this review for this previously approved drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No clinically significant or differential dose dependency (between the two treatment groups) was found for adverse events as the dose administered by SC and IV were the same.

7.5.2 Time Dependency for Adverse Events

No clinically significant time dependency for adverse events was found in the review..

7.5.3 Drug-Demographic Interactions

None found by this review.

7.5.4 Drug-Disease Interactions

No new information was found in this review for drug disease interaction.

7.5.5 Drug-Drug Interactions

Drug-drug interaction studies were not performed in the trial reviewed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable for this previously approved drug. No change to indication is proposed for this supplemental NDA.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable for this previously approved drug. No change to indication is proposed for this supplemental NDA.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric age group patients were enrolled in the clinical trials submitted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Doses of more than twice the recommended therapeutic dose in humans have been associated with acute onset of symptomatic hypotension and thrombocytopenia. Drug abuse potential is unlikely with anticancer agents with known toxicity profiles.

7.7 Additional Submissions / Safety Issues

There are no pertinent additional safety issues for review at this time associated with the indication/route of administration for which approval is being sought.
Follow up was completed prior to submission. Additional information was received in the form of safety updates. Post marketing, voluntary reports associated with Velcade (intravenous injection) include optic neuritis and blindness, cardiac adverse events (complete atrioventricular block, cardiac tamponade), ischemic colitis, encephalopathy, dysautonomia, bilateral deafness, disseminated intravascular coagulation, acute

pancreatitis, hepatitis, acute diffuse infiltrative pulmonary disease, reversible posterior leukoencephalopathy, toxic epidermal necrolysis, acute febrile neutrophilic dermatosis, herpes meningoencephalitis, optic neuropathy, blindness and ophthalmic herpes.

A safety update submitted on 4/29/2011 by the applicant, compared integrated safety of the SC and IV routes of administration from trials MMY-3021 and CAN-1004, which were consistent with the analyses of safety for the pivotal trial (MMY-3021) and, for the IV treatment groups, comparable to historic safety findings (using integrated data from 1356 subjects who received IV Velcade at a starting dose of 1.3 mg/m^2 from 8 completed trials in previously treated multiple myeloma, per Figure 9 below).

Figure 9 Historical Trials of IV Velcade with or without Dexamethasone in Subjects With Relapsed Multiple Myeloma

Study Number/ Acronym	Study Title	No. of treated subjects[a]
Phase 2 studies		
M34100-024[b]/ CREST	A Randomized, Open-Label Phase II Study of Two Doses of PS-341 Alone or in Combination with Dexamethasone in Patients with Multiple Myeloma Who Have Failed to Respond to or Relapsed Following Front-Line Therapy	26
M34100-025[b]/ SUMMIT	An Open-Label Phase II Study of PS-341 Alone or in Combination with Dexamethasone in Patients with Multiple Myeloma Who Have Relapsed Following Front-Line Therapy and are Refractory to Their Most Recent Therapy	202
M34101-029	A Phase 2, Open-Label, Extension Study to Provide PS-341 to Patients Who Previously Participated in a PS-341 Clinical Study and Who May Benefit from Re-treatment with or Continuation of PS-341 Therapy	NA[b]
Phase 3 studies		
M34101-039/ APEX	An International, Multicenter, Randomized, Open-Label Study of PS-341 Versus High-dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma	331
M34101-040[b]/ N/A	An International, Non-Comparative, Open-Label Study of PS-341 Administered to Patients with Multiple Myeloma who Received High-dose Dexamethasone in Millennium Protocol M34101-039 or Experienced Progressive Disease After Receiving at Least Four Previous Therapies	449
Study of VELCADE in combination with Doxil		
Phase 3		
DOXIL-MMY-3001/ N/A	A Randomized Controlled Study of DOXIL®/CAELYX® (doxorubicin HCL liposome injection) and VELCADE (bortezomib) or VELCADE Monotherapy for the Treatment of Relapsed Multiple Myeloma	318
VELCADE studies conducted in Japanese subjects		
Phase 1/2		
26866138-JPN-MM-101/201/ N/A	Phase 1/2 Study of JNJ-26866138 (bortezomib) in Japanese Patients with Relapsed or Refractory Multiple Myeloma	27
Phase 3		
26866138-JPN-MM-301 N/A	A Safety Confirmation Study of JNJ-26866138 (bortezomib) in Patients with Relapsed or Refractory Multiple Myeloma	3

[a] Totals represent only subjects treated with a starting dose of 1.3 mg/m^2 VELCADE.
[b] Subjects in extension Study M34101-029 are accounted for in the parent protocol (M34100-024, M34100-025, or M34101-040).
N/A=not applicable.

Source: Modified from applicant submission Summary of Clinical Safety-SC - *Module 2.7.4* page 18.

8 Postmarket Experience

There is no official postmarket experience with the subcutaneous route of administration of Velcade. See also Section 7.7, above, for safety update/postmarket experience pertaining to the intravenous Velcade formulation currently marketed. However, the applicant conducted a search of the Velcade Global Safety Database which retrieved 23 safety reports (individual case safety reports) in 23 patients who had received off-label

SC Velcade (and excluding safety results from trials MMY-3021 and CAN-1004); there was one fatality in this group of patients and 6 non-fatal SAEs, with 16 individual case safety reports considered nonserious; there were 3 cases of medication errors (accidental Velcade administration) among these cases (3 individual case safety reports). A review of the material submitted by the applicant (*Module 5, 5.3.6*) was consistent with the findings reported.

The single fatal case occurred in a 73 year old male with history of tuberculosis and prostate cancer who had received and been refractory to previous treatment (5 cycles of melphalan, prednisolone, and thalidomide and 2 doses of cyclophosphamide) for multiple myeloma diagnosed in 2008. This patient had received Velcade SC 1.3 mg/m^2 for 10 days in 2009 as part of a first cycle of treatment with Velcade SC and developed pneumonia 2 days after the last dose, after which his condition deteriorated and the patient expired after 2 days. The event of pneumonia was assessed and reported as possibly related to immune suppression from Velcade and dexamethasone.

Of the 6 nonfatal SAEs, 3 were reported as probably related to Velcade treatment. The 3 cases included: 1) a case of hypoesthesia following 1 dose of Velcade SC and paclitaxel which resulted in discontinuation of Velcade treatment; 2) a case of respiratory distress, requiring hospitalization, after administration of unknown number of doses of Velcade SC, which resolved in 3 days, and as a result of which Velcade treatment was discontinued; 3) a case of pathological hip fracture (grade 3) which was reported as not related to Velcade SC administration, and subsequent grade 3 wound infection reported as possibly related to Velcade SC and dexamethasone related immunosuppression. The remaining 3 cases reported as not related to SC Velcade included substernal chest pain attributed to GCSF, acute renal failure attributed to diarrhea induced dehydration and prior use of nonsteroidal anti-inflammatory drugs (in a patient with MDS), and cardiac failure attributed to the patient's pre-existing history of cardiac interventions (aortic valve replacement, pacemaker, coronary artery bypass).

Of the 16 cases of nonserious AE's, there were 3 cases of accidental Velcade SC administration in: 1) a patient with MDS (Velcade was administered instead of azacitidine) who experienced injection site reaction (erythema); 2) a patient with unknown diagnosis and renal failure (SC Velcade prepared for another patient was administered instead of epoetin alpha) in whom no AE was reported; 3) a patient with unknown diagnosis and asthma (a partial amount of SC Velcade was administered instead of Xolair) in whom no AE was reported. In 3 cases, the AEs experienced were consistent with the AEs associated with Velcade administration per the Velcade label and included hematoma, thrombocytopenia, erythema (in one patient with multiple myeloma), peripheral neuropathy (in one patient with MCL), and pruriginous uritcarial erythema (in a patient with unknown diagnosis). The remaining 9 cases included incorrect route of administration of drug and other drug administration errors with no associated AE reported.

These findings based on the off-label experience for SC are consistent with the known safety profile of Velcade and no new or pertinent safety signal was identified from the post market information submitted.

9 Appendices

9.1 Literature Review/References

1. Moreau P. et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study. *Lancet Oncol* 2011; 12: 431–40. Published on line April 19, 2011.

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3. Richardson PG, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 2003;348: 2609–17.

4. Jagannath S. et al. Updated survival analyses after prolonged follow-up of the phase 2, multicenter CREST study of bortezomib in relapsed or refractory multiple myeloma. *Br J Haematol* 2008; 1(434): 537-40.

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7. Richardson PG et al. Extended follow-up of a phase III trial in relapsed multiple myeloma: final time-to-event results from the APEX trial. *Blood* 2007; 110(10): 3557-60.

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9. Ogawa Y et al. Phase I and II pharmacokinetic and pharmacodynamic study of proteasome inhibitor bortezomib in Japanese patients with relapsed or refractory multiple myeloma. *Cancer Sci* 2008; 99 (1): 140-144.

10. European Medicines Agency. European public assessment reports. Retrieved November 14, 2011, from http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fep

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9.2 Labeling Recommendations

The proposed labeling by the applicant for the subcutaneous route of administration of this previously approved drug was found to be adequate. No additional labeling recommendations are deemed necessary from the clinical perspective. Upon approval of the subcutaneous route of administration, Velcade may be administered subcutaneously for all its current indications for which IV Velcade has been administered.

The proposed label as relating to the new subcutaneous route of administration for which this supplement was submitted and reviewed, provides for administration of Velcade subcutaneously for the same indications for which it is currently approved and labeled. The changes to the label will affect the section on RECENT MAJOR CHANGES (addition of SC route to the currently approved IV route of administration), the Dosing and Administration section (addition of SC alternative route of administration), pertinent admonishment in the DOSING AND ADMINISTRATION section for use of caution in calculating the volume to be administered given the difference in reconstituted concentrations, addition of pertinent information regarding preparation of the subcutaneous form of Velcade in the Reconstitution/Preparation for Intravenous Administration subsection, addition of clinically relevant information under the WARNINGS AND PRECAUTIONS section, Peripheral Neuropathy subsection, based on the data from the supplement for SC Velcade, and amendment of clinical studies and safety sections to include data from the SC Velcade supplement where pertinent and appropriate. Review of the label with the aforementioned changes, found the changes acceptable for the most part and the inclusion of the SC route of administration justified.

(b) (4)

The applicant will include the SC route of administration where administration is discussed in the label. The label will contain new tables for efficacy and safety data. The

safety data table and information submitted by the applicant for the label is adequate with minor alterations (on the order of 1-2% difference in certain adverse events compared to FDA's analyses of adverse event incidences). Evaluation of these differences, did not fully elucidate the source of the discrepancies and failed to fully confirm the sponsor's analysis. Analyses that included attribution of adverse events did not fully explain the differences between the FDA and applicant analyses.

The FDA analyses do not utilize attribution. The following are adverse events for which differences in incidence were found:

- Anemia, all grades in the SC arm which was reported by the applicant as 36% (n-53) and found by FDA to be 38% (n-56);
- Thromboctyopenia, grades 3 and 4 in the SC arm which was reported by the applicant as 8% (n=12) for grade 3 and found by the FDA to be 9% (n=13) and as 5% (n=7) for grade 4 and found by the FDA to be 5% (n=8);
- Nausea, all grades for SC arm which was reported by the applicant as 18% (n=27) and found by the FDA to be 19% (n=28);
- Asthenia, grade 3 in the SC arm which was reported by the applicant as 2% (n=3) and found by the FDA to be 3% (n=4);
- Fatigue, all grades in the IV arm which was reported by the applicant as 20% (n=15) and found by the FDA to be 21% (n=16);
- Pyrexia, all grade in the IV arm which was reported by the sponsor as 16% (n=12) and found by the FDA to be 19% (n=14);
- Herpes Zoster all grade in the SC arm which was reported by the applicant as 11% (n=16) and found by the FDA to be 12% (n=17);
- Herpes Zoster grade 3 in the SC arm which was reported by the applicant as 1% (n=2) and found by the FDA to be 2% (n=3);
- Weight decreased all grades in the IV arm which was reported by the applicant as 3% (n=2) and found by the FDA to be 4% (n=3).

These changes have been made to the applicant's proposed table summarizing the incidence of adverse events (Table 43 Most Commonly Reported Adverse Events ≥ 10% with Grade 3 and ≥ 4 Intensity in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs IV and are reflected in the table modified based on FDA analysis, Table 43 below.

The label, appropriately, does not provide for self administration of SC Velcade as this was not evaluated in the trial which forms the basis of approval for SC Velcade as a new/alternative route of administration.

Table 43 Most Commonly Reported Adverse Events ≥ 10% with Grade 3 and ≥ 4 Intensity in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs IV

	Subcutaneous (N147) (a)			IV (N=74) (a)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
MedDRA Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Blood and lymphatic system disorders						
Anaemia	53 (36)	14 (10)	4 (3)	26 (35)	6 (8)	0
Leukopenia	29 (20)	9 (6)	0	16 (22)	4 (5)	1 (1)
Neutropenia	42 (29)	22 (15)	4 (3)	20 (27)	10 (14)	3 (4)
Thrombocytopenia	52 (35)	12 (8)	7 (5)	27 (36)	8 (11)	6 (8)
Gastrointestinal disorders						
Abdominal pain	5 (3)	1 (1)	0	8 (11)	0	0
Abdominal pain upper	3 (2)	0	0	8 (11)	0	0
Constipation	21 (14)	1 (1)	0	11 (15)	1 (1)	0
Diarrhea	35 (24)	2 (1)	1 (1)	27 (36)	3 (4)	1 (1)
Nausea	27 (18)	0	0	14 (19)	0	0
Vomiting	17 (12)	3 (2)	0	12 (16)	0	1 (1)
General disorders and administration site conditions						
Asthenia	23 (16)	3 (2)	0	14 (19)	4 (5)	0
Fatigue	17 (12)	3 (2)	0	15 (20)	3 (4)	0
Pyrexia	28 (19)	0	0	12 (16)	0	0
Infections and infestations						
Herpes zoster	16 (11)	2 (1)	0	7 (9)	1 (1)	0
Investigations						
Weight decreased	22 (15)	0	0	2 (3)	1 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	14 (10)	0	0	7 (9)	0	0
Musculoskeletal and connective tissue disorders						
Back pain	21 (14)	1 (1)	0	8 (11)	1 (1)	1 (1)
Pain in extremity	8 (5)	1 (1)	0	8 (11)	2 (3)	0
Nervous system disorders						
Headache	5 (3)	0	0	8 (11)	0	0
Neuralgia	35 (24)	5 (3)	0	17 (23)	7 (9)	0
Peripheral neuropathies NEC (b)	56 (38)	8 (5)	1 (1)	39 (53)	11 (15)	1 (1)
Psychiatric disorders						
Insomnia	18 (12)	0	0	8 (11)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	11 (7)	2 (1)	0	9 (12)	2 (3)	0
Vascular disorders						
Hypertension	14 (10)	3 (2)	0	3 (4)	0	0

(a) Safety population: 147 patients in the subcutaneous treatment and 74 patients in the IV treatment who received at least 1 dose of study medication
(b) Represents MedDRA high level term

Source: Applicant's proposed label.

Table 44 Most Commonly Reported Adverse Events (≥ 10%), with Grade 3 and ≥ 4 Intensity in the Relapsed Multiple Myeloma Study (N=221) of Velcade Subcutaneous Compared With Intravenous

	Subcutaneous (N=147) (a)			Intravenous (N=74) (a)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
MedDRA Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Blood and lymphatic system disorders						
Anaemia	56 (38)	14 (10)	4 (3)	26 (35)	6 (8)	0
Leukopenia	29 (20)	9 (6)	0	16 (22)	4 (5)	1 (1)
Neutropenia	42 (29)	22 (15)	4 (3)	20 (27)	10 (14)	3 (4)
Thrombocytopenia	52 (35)	13 (8)	8 (6)	27 (36)	8 (11)	6 (8)
Gastrointestinal disorders						
Abdominal pain	5 (3)	1 (1)	0	8 (11)	0	0
Abdominal pain upper	3 (2)	0	0	8 (11)	0	0
Constipation	21 (14)	1 (1)	0	11 (15)	1 (1)	0
Diarrhea	35 (24)	2 (1)	1 (1)	27 (36)	3 (4)	1 (1)
Nausea	28 (19)	0	0	14 (19)	0	0
Vomiting	17 (12)	3 (2)	0	12 (16)	0	1 (1)
General disorders and administration site conditions						
Asthenia	23 (16)	4 (3)	0	14 (19)	4 (5)	0
Fatigue	17 (12)	3 (2)	0	16 (21)	3 (4)	0
Pyrexia	28 (19)	0	0	14 (19)	0	0
Infections and infestations						
Herpes zoster	17 (12)	3 (2)	0	7 (9)	1 (1)	0
Investigations						
Weight decreased	22 (15)	0	0	3 (4)	1 (1)	0
Metabolism and nutrition disorders						
Decreased appetite	14 (10)	0	0	7 (9)	0	0
Musculoskeletal and connective tissue disorders						
Back pain	21 (14)	1 (1)	0	8 (11)	1 (1)	1 (1)
Pain in extremity	8 (5)	1 (1)	0	8 (11)	2 (3)	0
Nervous system disorders						
Headache	5 (3)	0	0	8 (11)	0	0
Neuralgia	35 (24)	5 (3)	0	17 (23)	7 (9)	0
Peripheral neuropathies NEC (b)	56 (38)	8 (5)	1 (1)	39 (53)	11 (15)	1 (1)
Psychiatric disorders						
Insomnia	18 (12)	0	0	8 (11)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	11 (7)	2 (1)	0	9 (12)	2 (3)	0
Vascular disorders						
Hypertension	14 (10)	3 (2)	0	3 (4)	0	0

(a) Safety population: 147 patients in the subcutaneous treatment and 74 patients in the IV treatment who

received at least 1 dose of study medication
(b) Represents MedDRA high level term
Source: Modified from applicant's proposed label.

(b) (4)

The applicant has included secondary endpoints, including exploratory ones in the proposed label. (b) (4)

Reviewer comment: (b) (4)

secondary and exploratory endpoints should not be included in the efficacy table. If these are included in the label, (b) (4)

(b) (4)

(b) (4)

Table 46 Summary of Efficacy Analysis in the Relapsed Multiple Myeloma Study of Velcade Subcutaneous Compared With Intravenous

(b) (4)

Reviewer comment: (b) (4) *There are various formatting changes recommended for the label, including writing out the word "intravenous" rather than IV in the table headers given that the word "subcutaneous" is also fully spelled and does not appear as "SC" in the table headers; this is for consistency.*

QT-IRT recommends that following language in the label:

Section 12.2:
The effect of a single dose of bortezomib 1.3 mg/m^2 following intravenous or subcutaneous administration was evaluated in an open-label, phase I study in 24 subjects with measurable and symptomatic multiple myeloma. No large changes in mean QTc interval (i.e., >20 ms) from baseline were detected. Because of the design limitations, small increase in mean QT interval (i.e., <10 ms) cannot be ruled out.

9.3 Advisory Committee Meeting

No advisory committee was necessary for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FIROOZEH ALVANDI
12/09/2011

VIRGINIA E KWITKOWSKI
12/09/2011
Concur.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21602 **Applicant: Millenium** **Stamp Date: March 23, 2011**

Drug Name: VELCADE® (bortezomib) for Injection **NDA/BLA Type: sNDA Supplement 027**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			Electronic eCTD submission.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: Study 26866138-MMY-3021	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Phase 3, open label randomized, non-inferiority study of subcutaneous and intravenous Velcade in adult subjects (age >18 years) with previously treated multiple myeloma who had received 1 to 3 prior lines of therapy and had measurable evidence of disease progression since their last previous therapy. Indication: Previously treated multiple myeloma (with measurable evidence of disease progression since last previous therapy).				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			Received after submission based on information request from FDA.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	Initially approved prior to QT testing regulation.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	A trial in response to Written Request for pediatric studies has been initiated.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		Received after submission based on information request from FDA.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?		x		Only derived "analysis" datasets provided. Raw datasets needed for complete analysis.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		x		Only derived "analysis" datasets provided. Raw datasets needed for complete analysis.
CASE REPORT FORMS					

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?		x		Financial disclosure could not be obtained from 10 investigators for reasons of "no longer at site", "maternity leave", no response", and "no longer PI, not applicable". The Sponsor did not provide details of how they demonstrated due diligence in attempting to obtain this information.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes**____**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Only derived "analysis" datasets were provided. Raw datasets should be submitted for efficacy and safety.

2. No financial disclosure was provided for 10 investigators. You did not provide details of how you demonstrated due diligence in attempting to obtain this information.

Firoozeh Alvandi, MD 04/6/2011

Reviewing Medical Officer Date

Virginia, Kwitkowski, MS, RN, ACNP-BC Acting Clinical Team Leader 04/07/2011

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FIROOZEH ALVANDI
05/12/2011

VIRGINIA E KWITKOWSKI
05/17/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

CHEMISTRY REVIEW(S)

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION I, BRANCH III

Review of Chemistry, Manufacturing, and Controls

Clinical Review Division: Oncology Products (HFD-150)

NDA#: 21-602	**REVIEW#.** 1	**REVIEW DATE:**	12/07/2011
SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED**
SE2-027 (PA)	03/23/2011	03/23/2011	03/30/2011
AMENDMENT	**PDUFA GOAL**		
10/04/2011	01/23/2012		

NAME & ADDRESS OF APPLICANT: Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Dipen Chemburkar, Senior CMC Manager
Regulatory Affairs
Phone: (617) 444-2225
Fax: (617) 551-3742

DRUG PRODUCT NAME

Proprietary:	VELCADE® for Injection
Nonproprietary/USAN:	bortezomib
Code Name#:	PS-341
Chem. Type:	
Ther. Class:	

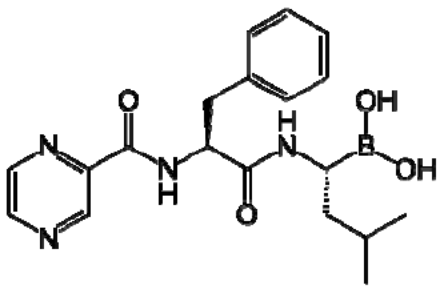
PHARMACOLOGICAL CATEGORY/INDICATION: multiple myeloma and mantle cell lymphoma

DOSAGE FORM: Lyophilized powder for injection
STRENGTH: 3.5 mg

ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ Rx ___ OTC
SPECIAL PRODUCTS: ___ Yes _X_ No
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

Chemical Name: (b) (4)

Molecular Formula: $C_{19}H_{25}BN_4O_4$
Molecular Weight: 384.24



REMARKS/COMMENTS:

The Prior-Approval supplement provides for the subcutaneous route of administration as an alternative to the existing intravenous one. The applicant states that all aspects of manufacturing and release of the drug product vials remain unchanged from the currently approved intravenous dose. The release and stability specifications have been assessed and are applicable in their current form for release for use both as IV and SC dosing. The currently approved IV dose schedule allows for reconstitution of the drug product lyophilized cake with 3.5 mL 0.9% Sodium Chloride for Injection for a final concentration of 1.0 mg/mL. The proposed SC dose schedule allows for reconstitution of the drug product lyophilized cake with 1.4 mL for a final concentration of 2.5 mg/mL. This review focuses on the in-use stability of the reconstituted solution and its the compatibility with various syringes.

Three types of commercial syringes from different vendors were tested during the compatibility study, with the reconstituted drug product (2.5 mg/mL, Lot ZC070A) in the syringes being held for up to (b) (4) at room temperature in ambient light. The reconstituted solution was assessed for color and clarity of solution, particulate (visual), pH, assay, and impurities. After 8 hours of storage at room temperature with ambient light, no significant change was observed in any of the syringes. After (b) (4) storage, slight increase in the total impurities was observed primarily due to the increase in the level of impurities (b) (4), but still well with drug product specifications. Based on the results, the reconstituted drug product solution (2.5 mg/mL) for subcutaneous injection appears to be compatible with the commercial syringes tested.

In-use stability studies of the 2.5 mg/mL reconstituted solution were conducted in both syringes and vials, with three lots of drug product for each. In addition to the compatibility, two other lots of drug product were used for the in-use stability study of the reconstituted drug product in syringes, Lot 9EZT000 and Lot 100797. The reconstituted drug product of these two lots was stored (b) (4), and room temperature with exposure to ambient light (b) (4). After (b) (4) storage, no significant change was observed (b) (4). After (b) (4) under room temperature with exposure to ambient light, slight increase in the total impurities level was observed due to the increase in the level of impurities (b) (4), however, both items are still well with specifications. The same three lots of reconstituted drug product (Lots ZC070A, 9EZT001, 100797) were used for the in-use stability study in vials. Similarly, the drug product solution was held for up to (b) (4) room temperature with exposure to ambient light. Similar results were observed comparing to the study in syringes, with essentially no change when the reconstituted drug product was stored (b) (4) and slight increase in the total impurities level due to impurities (b) (4). Therefore, the in-use stability studies support the proposed maximum storage duration of 8 hours under room temperature and ambient light in the labeling in Section 2.8.

There are no other proposed CMC related changes in the package insert. An amendment was submitted on 10/04/2011 for carton and immediate container labeling for both routes of administration (intravenous and subcutaneous), together with the sticker insert. No CMC related changes were made to the carton and immediate container labeling. Upon communication with

the DMEPA reviewer, Dr. Terri Wood-Cummings, the DMEPA review will cover these changes in the carton and immediate container labeling addressing the two routes of administration. The immediate container and carton labeling as well as the sticker insert appear acceptable from CMC perspective.

The applicant also requests for categorical exclusion from environmental assessment as per 21 CFR 25.31(b). It is claimed that no extraordinary circumstances exist which would results in significant impact to the environment from the discharge of this substance. The request may be granted.

Dr. Jessica Cole from Product Quality Microbiology reviewed the supplement with an NAI on 11/10/2011.

Overall, the supplement is recommended for approval from CMC standpoint.

CONSULT REVIEW:

Dr. Jessica Cole from Product Quality Microbiology reviewed the supplement with an NAI on 11/10/2011. Her review conclusion is that the proposed hold time (8 hours) in saline is acceptable.

COMMENTS TO BE CONVEYED TO APPLICANT: N/A

CONCLUSIONS & RECOMMENDATIONS:

The supplement is recommended for approval from CMC standpoint.

(see attached electronic signature page)

Zedong Dong, Ph.D.
Review Chemist
cc: Orig. NDA#21-602
HFD-150/Division File
ONDQA/DIV I/PM/SGoldie
ONDQA/DIV I/ChemBranchChf/HPatel
ONDQA/DIV I/Chem/ZDong

REVIEW NOTES AND ASSESSMENTS

The Prior-Approval supplement provides for the subcutaneous route of administration as an alternative to the existing intravenous one. To complement the IV route of administration, Millennium seeks the approval of a subcutaneous route of administration for VELCADE that, in addition to adding convenience and benefiting patients with poor venous access, has been shown to provide a more favorable safety profile with, in particular, reduced peripheral neuropathy.

The applicant states that all aspects of manufacturing and release of the drug product vials remain unchanged from the currently approved intravenous dose. The release and stability specifications have been assessed and are applicable in their current form for release for use both as IV and SC dosing. The currently approved IV dose schedule allows for reconstitution of the drug product lyophilized cake with 3.5 mL 0.9% Sodium Chloride for Injection for a final concentration of 1.0 mg/mL. The proposed SC dose schedule allows for reconstitution of the drug product lyophilized cake with 1.4 mL for a final concentration of 2.5 mg/mL.

CMC information submitted in the supplement includes: (1) Compatibility of the reconstituted drug product with various common syringes; (2) In-use stability of the reconstituted solution.

Since relevant information has been reviewed previously for the 1 mg/mL reconstituted drug product for intravenous administration, this review focuses on the newly generated information for the 2.5 mg/mL drug product for subcutaneous administration.

1. Compatibility of the 2.5 mg/mL reconstituted drug product with syringes

ACCEPTABLE

Three types of commercial syringes from different vendors were tested during the compatibility study, with the reconstituted drug product (2.5 mg/mL) in the syringes being held for up to (b) (4) at room temperature in ambient light. The reconstituted drug product (Lot ZC070A) was assessed for color and clarity of solution, particulate (visual), pH, assay, and impurities. After 8 hours of storage at room temperature with ambient light (which is the maximum storage duration as defined in the drug product labeling), no significant change was observed in any of the syringes. After (b) (4) storage, slight increase in the total impurities was observed primarily due to the increase in the level of impurities (b) (4), but still well with drug product specifications. Based on the results, the reconstituted drug product solution (2.5 mg/mL) for subcutaneous injection appears to be reasonably compatible with the commercial syringes tested. The results for the compatibility study are summarized in Table 1 in this review.

Table 1. Syringe Compatibility Testing Results (2.5 mg/mL)

	Baseline Control	Reconstituted PS-341 in Syringe[c] from Vendor 1		Reconstituted PS-341 in Syringe[d] from Vendor 2		Reconstituted PS-341 in Syringe[e] from Vendor 3	
		Test Syringe (RT, ambient light)		Test Syringe (RT, ambient light)		Test Syringe (RT, ambient light)	
Test	Initial	8 hr	(b) (4)	8 hr	(b) (4)	8 hr	(b) (4)
Color/Clarity of Solution	Conforms[a]	Conforms[a]		Conforms[a]		Conforms[a]	
Particulates (visual)	Conforms[b]	Conforms[b]		Conforms[b]		Conforms[b]	
pH	4.5	4.5		4.5		4.5	
Mean Assay by HPLC (%) (n=3)	(b) (4)						
Total Impurities by HPLC (% w/w)	(b) (4)						
Specified Known Impurities by HPLC (% w/w):							
(b) (4)							

a Clear, colorless solution
b Essentially free from particles or foreign matter
c Syringe composed of polypropylene barrel, polypropylene stopper/gasket, and silicone lubricant
d Syringe composed of polypropylene barrel, polypropylene stopper/gasket, and silicone lubricant
e Syringe composed of polypropylene barrel, Latex-free elastomer stopper/gasket, and silicone lubricant

2. <u>In-use stability of the 2.5 mg/mL reconstituted solution</u> **<u>ACCEPTABLE</u>**

In-use stability studies of the 2.5 mg/mL reconstituted solution were conducted in both syringes and vials, with three lots of drug product for each.

In addition to the study carried out in Table 1, which also serves the purpose of in-use stability study in syringes, two other lots of drug product were used for the in-use stability study of the

reconstituted drug product in syringes, Lot 9EZT000 and Lot 100797. The reconstituted drug product of these two lots was stored (b) (4) and room temperature with exposure to ambient light (b) (4). After (b) (4) storage, no significant change was observed when the drug product solution was stored (b) (4). (b) (4) under room temperature and ambient light, slight increase in the total impurities level was observed due to the increase in the level of impurities (b) (4), however, both items are still well with specifications. The study results for Lot 100797 are summarized in Table 2.

Table 2. In-Use Stability Study for Reconstituted Lot 100797 in Syringes (2.5 mg/mL)

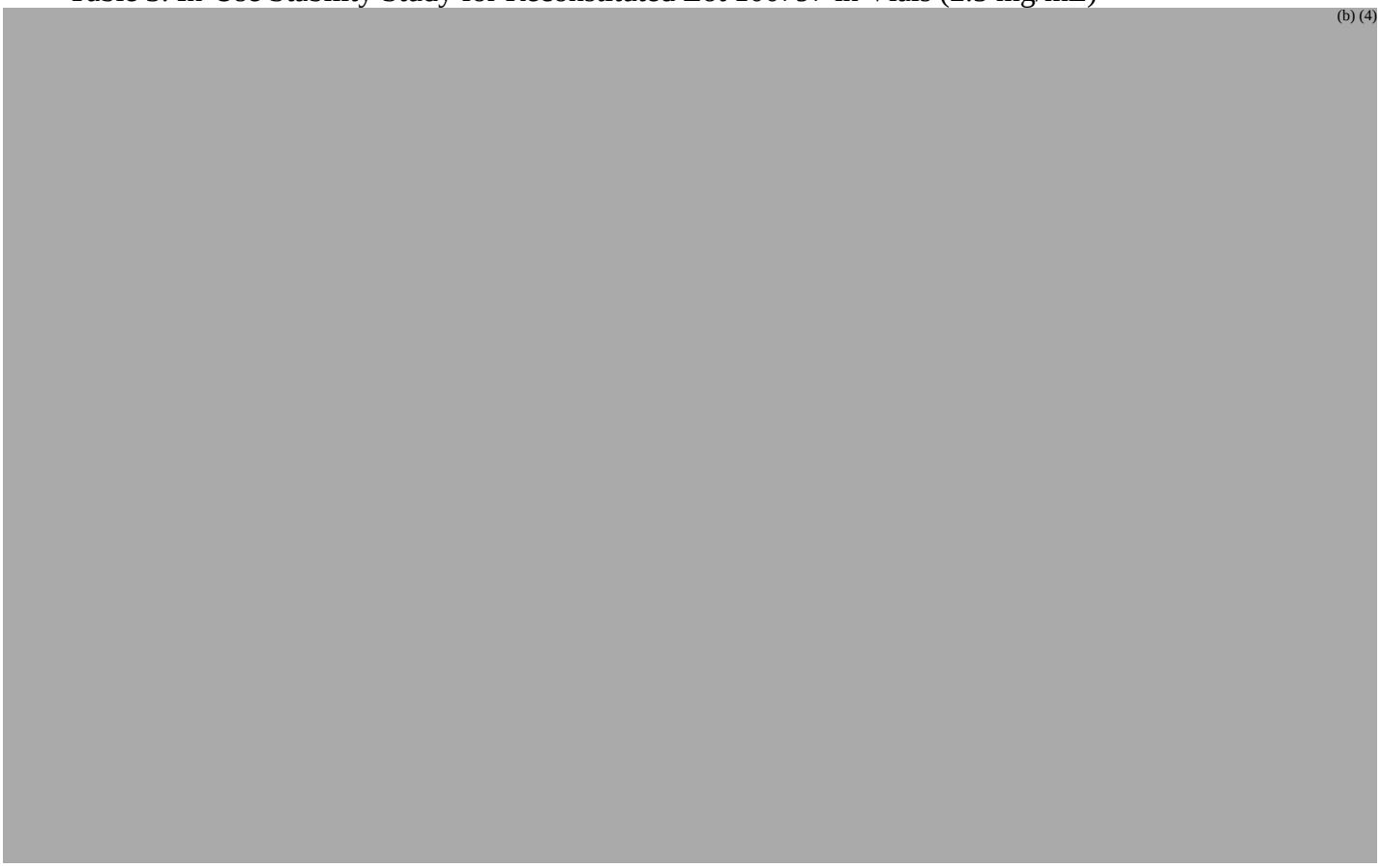
(b) (4)

Three lots of reconstituted drug product (Lots ZC070A, 9EZT001, 100797) were used for the in-use stability study in vials. The drug product solution was held for up to (b) (4) room temperature with exposure to ambient light. Similar results were observed comparing to the study in syringes, with essentially no change when the reconstituted drug product was stored (b) (4) and slight increase in the total impurities level due to impurities (b) (4). The representative results for Lot 100797 are summarized in Table 3 in this review.

The in-use stability studies carried out for the reconstituted drug product (2.5 mg/mL) in syringes and vials support the proposed maximum storage duration of 8 hours under room temperature and ambient light in the labeling.

Table 3. In-Use Stability Study for Reconstituted Lot 100797 in Vials (2.5 mg/mL)

(b) (4)



3. Labeling changes **ACCEPTABLE**

There are no proposed CMC related changes in Section 3 (Dosage Forms and Strengths), Section 11 (Description), or Section 16 (How Supplied/Storage and Handling) in the package insert.

When stored at 25°C (77°F) with exposure to normal indoor lighting, the proposed maximum storage duration of 8 hours for the reconstituted drug product in the original vials and/or syringes prior to administration in Section 2.8 (Reconsitution/Preparation for Intravenous and Subcutaneous Administration) of the labeling appear acceptable as supported by the in-use stability studies.

An amendment was submitted on 10/04/2011 for carton and immediate container labeling for both routes of administration, together with the sticker insert. No CMC related changes were made to the labeling. Upon communication with the DMEPA reviewer, Dr. Terri Wood-Cummings, the DMEPA review will cover these changes in the carton and immediate container labeling. The immediate container and carton labeling as well as the sticker insert appear acceptable from CMC perspective.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

4. Product Quality Microbiology consult review **ACCEPTABLE**

Dr. Jessica Cole from Product Quality Microbiology reviewed the supplement with an NAI on 11/10/2011. Her review conclusion is that the proposed hold time (8 hours) in saline is acceptable.

5. Other comments

The applicant also requests for categorical exclusion from environmental assessment as per 21 CFR 25.31(b). It is claimed that no extraordinary circumstances exist which would results in significant impact to the environment from the discharge of this substance. The request may be granted.

Overall, the supplement is recommended for approval from CMC standpoint.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZEDONG DONG
12/13/2011

HASMUKH B PATEL
12/13/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	21-602
Supporting document/s:	SDN 278, Supplement 27
Applicant's letter date:	March 23, 2011
CDER stamp date:	March 23, 2011
Product:	Bortezomib
Indication:	Multiple myeloma and mantle cell lymphoma
Applicant:	Millennium Pharmaceuticals, Inc.
Review Division:	Division of Hematology Oncology Products
Reviewer:	Wei Chen, Ph.D.
Supervisor/Team Leader:	Haleh Saber, Ph.D.
Division Director:	John Leighton, Ph.D.
Project Manager:	Amy Baird

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21,602 are owned by Millennium Pharmaceuticals, Inc or are data for Millennium Pharmaceuticals, Inc has obtained a written right of reference.
Any information or data necessary for approval of NDA 21,602 that Millennium Pharmaceuticals, Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 21,602.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Bortezomib (VELCADE®) is a proteasome inhibitor. Bortezomib, administered as an intravenous (IV) bolus injection, was approved in 2003 in the United States (US) for the treatment of multiple myeloma and later for the treatment of mantle cell lymphoma in patients who have received at least 1 prior therapy. Bortezomib is approved in several countries including European Union. The Applicant is now seeking the approval for the subcutaneous route of administration. Results of two repeat-dose studies in monkey and a local tolerance study in rabbit are submitted to support the change in the route of administration. The 4-cycle subcutaneous and intravenous injection comparative toxicity/ PK study in cynomolgus monkey is considered as the pivotal study and reviewed for the approvability of this sNDA. Results of the study indicate that toxicities are comparable for the SC and IV route of administration and that the PK is also comparable with the exception of lower C_{max} observed for SC dosing in cycle 1 as compared to the IV administration (as seen in blood or plasma). The significance of the difference in the exposure is unclear as this trend was not evident in other dosing cycles.

1.2 Brief Discussion of Nonclinical Findings

A. Brief overview of nonclinical findings

The pivotal non-clinical toxicity study of bortezomib in support of this supplemental NDA was conducted in cynomolgus monkey, consistent with the clinical dose regimen. Toxicities and systemic exposures of bortezomib were investigated after bortezomib was administered subcutaneously (SC) or intravenously (IV) to monkeys. The dose (1.2 mg/m^2) used in the study for the comparison of subcutaneous administration and intravenous administration is close to the clinical dose (1.3 mg/m^2).

The toxicokinetic (TK), and toxicity profiles of bortezomib with subcutaneous administration were comparable to those with intravenous administration. No new toxicologic findings were noted after administration via SC route.

Bortezomib was rapidly absorbed after SC administration. The time-dependent changes in the exposures were generally similar after SC or IV administration of bortezomib. For both administration routes, C_{max} and AUC values in blood were higher than those observed in plasma; this may be related to the distribution of bortezomib to RBCs. In general. SC and IV administration of bortezomib resulted in comparable PK profiles, with the exception of lower C_{max} after SC dosing in Cycle 1 of the study as compared to the results obtained for Cycle 1 IV administration. This trend was not observed in the following dosing cycles.

The local tolerance study is not reviewed. Based on the summary data, there were no test article-related microscopic changes at the injection sites when bortezomib was administered subcutaneously.

B. Pharmacologic activity

The effect of SC administration of bortezomib on tumor burden was evaluated in a 5T2MM mouse model. SC administration of bortezomib at 0.6 mg/kg (1.8 mg/m^2) or 0.8 mg/kg (2.4 mg/m^2), twice weekly (BIW), significantly decreased the tumor burden in a 5T2MM myeloma mouse model by reducing the number of plasma cells and serum paraprotein levels, and decreasing angiogenesis and MM bone disease (Cited paper by Deleu S. et al., Bortezomib alone or in combination with the histone deacetylase inhibition JNJ-26481585: effect on myeloma bone disease in the 5T2MM murine model of myeloma).

C Nonclinical safety issues relevant to clinical use

There are no new safety concerns related to SC administration of the drug.

See the approved label for bortezomib-related toxicities.

1.3 Recommendations

1.3.1 Approvability

Recommending approval. The non-clinical studies adequately support the safety of bortezomib by subcutaneous route of administration.

1.3.2 Additional Non Clinical Recommendations

Additional non-clinical studies are not needed at this time.

1.3.3 Labeling

No changes to the non-clinical sections of the label are proposed with this application; therefore no labeling review is deemed necessary.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 179324-69-7

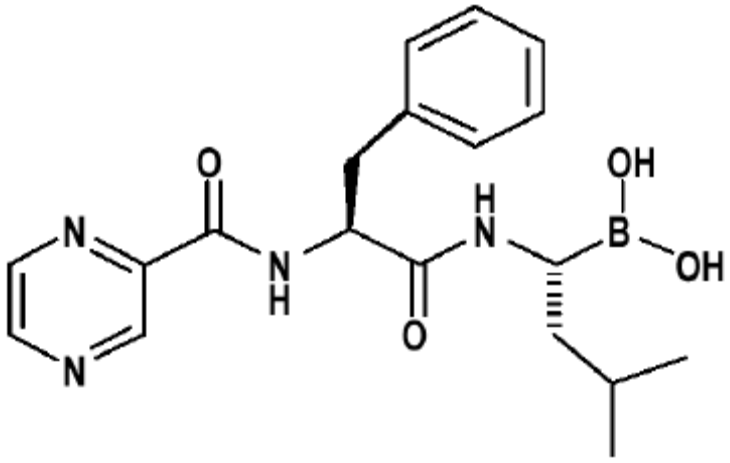
Generic Name: Bortezomib

Code Name: PS-341

Chemical Name: N-(2-pyrazinecarbonyl)-L-phenylalanine-L-leucine boronic acid

Molecular Formula/Molecular Weight: C19H25BN4O4 / 384.24

Structure or Biochemical Description:



Pharmacologic Class: Proteasome inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs: IND 56,515

2.3 Drug Formulation: 3.5 mg/vial, reconstitute with 1.4 ml 0.9 % Sodium Chloride to final concentration of 2.5 mg/mL

2.4 Comments on Novel Excipients: none

2.5 Comments on Impurities/Degradants of Concern: none

2.6 Proposed Clinical Population and Dosing Regimen:

- Treatment of patients with multiple myeloma
- Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy

Refer to the approved drug label for dosing regimens for different indications, The Applicant is not proposing to change the dose of bortezomib for SC administration.

Studies Submitted

3.1 Studies Reviewed

Repeat dose

	Title	Study No	Fold/file name
1	Velcade (Bortezomib): A 4-Cycle Subcutaneous and Intravenous Injection Toxicity Study in Cynomolgus Monkey	TOX7345	Module 4.2.3.2

3.2 Studies Not Reviewed

Repeat dose

	Title	Study No	Fold/file name
1	An 8-Week Subcutaneous Toxicity Study of Velcade in Cynomolgus Monkeys	TOX8394	Module 4.2.3.2

Local tolerance study

	Title	Study No	Fold/file name
1	Local tolerability / tissue reaction study of Velcade™ in female New- Zealand White rabbits following a single subcutaneous injection	TOX6863	Module 4.2.3.6

3.3 Previous Reviews Referenced: none

4 Pharmacology: no study submitted

4.1 Primary Pharmacology: no study submitted

4.2 Secondary Pharmacology: no study submitted

4.3 Safety Pharmacology: no study submitted

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME: no study submitted

5.2 Toxicokinetics:

See section below for repeat-dose toxicity study with TK

6 General Toxicology

6.1 Single-Dose Toxicity: no study submitted

6.2 Repeat-Dose Toxicity

Study title: Velcade (Bortezomib): A 4-Cycle Subcutaneous and Intravenous Injection Toxicity Study in Cynomolgus Monkey

Study no.: (b) (4)

Study report location: (b) (4)

Conducting laboratory and location: (b) (4)

Date of study initiation: January 5, 2006

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: bortezomib
Lot number: YB005A1
Purity: 99.8%

Key Study Findings

- TK and toxicity profiles with SC route were similar to those with IV administration;
- Mortalities were observed at 0.166 mg/kg SC;
- Major treatment-related toxicities were emesis and diarrhea, body weight losses, alterations in serum biochemistry parameters and microscopic lesions in the peripheral nerve system and spinal cord, kidneys, bone and immune system;

- The hematologic changes were generally reversible; the reversibility of other changes were not evaluated in the study;
- The bioavailability in blood following subcutaneous dosing at 0.1 mg/kg was almost 100% when comparing to AUC exposure following IV dosing at 0.1 mg/kg;
- Plasma exposures at 0.1 mg/kg were higher (~150%) with IV administration on day 1, but lower (63%-74%) with IV administration on day 32 and day 74.

Methods

Doses:	SC: 0, 0.075, 0.1, 0.166 mg/kg IV: 0.1 mg/kg
Frequency of dosing:	SC (Control, LD, MD), and IV: Cycle 1, 2, and 3: dosing on days 1, 4, 8 and 11, followed by 1 week of recovery Cycle 4: dosing on days 1, 4, 8 and 11 with terminal euthanasia 72 hours after the last dose. Duration of cycle: 21 days SC in HD: Once weekly dosing for 12 weeks with terminal euthanasia 72 hours after the last dose
Route of administration:	SC for groups 1-4 (control, LD, MD, HD) IV for group 5
Dose volume:	SC: 3.5 mg/mL IV: 1 mg/mL
Formulation/Vehicle:	0.9% Sodium Chloride for Injection USP
Species/Strain:	cynomolgus monkey
Number/Sex/Group:	3 sex/group
Age:	2.5-3 years
Weight:	male: 2.0-2.8 kg; female: 2.1-2.5 kg
Satellite groups:	for toxicokinetics: 6 /sex/group for control, MD, HD 4/sex for LD
Unique study design:	none
Deviation from study protocol:	none

HD: high-dose; IV: intravenous; LD: low-dose; MD: mid-dose; SC: subcutaneous

Observations and times

Mortality: daily

Clinical Signs: twice daily for mortality and sign of ill, daily for a detailed examination

Injection site evaluation: predose on dosing day

Neurological assessment: pretreatment and during week 10

Body weights: pretreatment, and weekly thereafter

Food consumption: daily by visual inspection

Ophthalmoscopy: pretreatment and during week 11

EKG: pretreatment and day 72

Hematology: pretreatment and Days 14, 35 and 77 for groups 1, 2, 3, and 5
Pretreatment and days 11, 32, 53 and 81 for group 4

Clinical chemistry: pretreatment and Days 14, 35 and 77 for groups 1, 2, 3, and 5
Pretreatment and days 11, 32, 53 and 81 for group 4

Urinalysis: days 14, 21, 35, 42, 63 and 77 for groups 1, 2, 3 and 5
Days 11, 14, 32, 35, 53, 56, 77 and 81 for group 4

Gross pathology: all animals at necropsy

Organ weights: all animals at necropsy

Histopathology: all animals at necropsy

Toxicokinetics:

Groups 1, 2, 3 and 5: days 1, 32 and 74;
- Day 1 (first dose of cycle 1): predose, 7, 15 and 30 minutes, and again at 1, 2, 4, 8, 12, 24, 48 and 72 hours postdose
- Day 32 (dose 8 or 4th dose of cycle 2): predose, 7 and 30 minutes, and again at 1, 2, 4, 24 and 72 hours postdose
- Day 74 (dose 16 or 4th dose of cycle 4): predose, 7, 15 and 30 minutes, and again at 1, 2, 4, 8, 12, 24, 48 and 72 postdose

Group 4: days 1, 50 and 78
- Day 1 (dose 1): predose, 7, 15 and 30 minutes and at 1, 2, 4, 8, 12, 24, 48 and 72 hours postdose
- Day 50 (dose 8): predose, 7 and 30 minutes and at 1, 2, 4, 24 and 72 hours postdose
- Day 78 (dose 12): predose, 7, 15 and 30 minutes and at 1, 2, 4, 8, 12, 24, 48 and 72 hours postdose

Results

Mortality: 2 in group 4 (HD, 0.166 mg/kg, SC)

#401: male, found dead on day 79, the day after receiving the 12th weekly dose
Cause of death: undetermined
#453: female, found dead on day 72, the day after administration of the 11th weekly dose
Cause of death: undetermined, possibly from secondary infection

Clinical signs:

Early death

#401: chronic soft/liquid feces and/or emesis (often characterized by the presence of discolored and/or mucoid material in the cage tray) following dose administration.

#453: repeated transient episodes of decreased activity, reduced body temperature, and reduced appetite following each weekly dose administration. These findings were accompanied by multiple clinical signs indicative of deteriorating condition, including: vocalization, sunken eyes, dehydration, pallor of gums or skin, soft/liquid feces and/or emesis (often characterized by the presence of discolored material in the cage tray), prominent backbone, hunched posture, thinness and decreased muscle tone.

All animals

Sex	Male					Female				
Group	1	2	3	4	5	1	2	3	4	5
No. of animals per group	3	3	3	3	3	3	3	3	3	3
Route of administration	sc				iv	sc				iv
Dose (mg/kg)	0	0.075	0.1	0.166	0.1	0	0.075	0.1	0.166	0.1
Abdominal distension Moderate										1
Abdominal distension Slight				1						2
Abnormal gait			1	1					1	
Activity decreased			1	2	2			1	3	
Anus Dilated									1	
Anus discharge mucoid red					1					
Backbone prominent				1					1	
Cold to touch				1					1	
Dehydrated moderate									1	
Dehydrate slight								1		
Eye partly closed\left					1					
Feces absent				1					1	
Feces liquid moderate								1		2
Feces liquid moderate suspected								3	1	
Feces liquid severe									1	
Feces liquid slight								3	3	
Feces liquid slight										

Sex	Male					Female				
Group	1	2	3	4	5	1	2	3	4	5
No. of animals per group	3	3	3	3	3	3	3	3	3	3
Route of administration	sc				iv	sc				iv
Dose (mg/kg)	0	0.075	0.1	0.166	0.1	0	0.075	0.1	0.166	0.1
suspected								3	3	
Feces soft moderate suspected			3							3
Feces soft severe					1			1	1	
Feces soft slight		2	1		2					
Feces soft slight Suspected			3	3	3				3	3
Food partly digested Slight					1					
Food partly digested severe									1	
Fur erected				1						
Fur staining brown/tail								2	1	
Fur staining brown\urogenital								1	1	
Fur staining red\inguinal left			1	1						
Fur staining red\inguinal right				1						
Fur staining red\urogenital										1
Fur staining yellow\abdominal				1						
Fur staining yellow\inguinal left				1						
Fur staining yellow\inguinal right				1						
Fur staining yellow\urogenital				1						
Fur thin cover\dorsal thoracic					1					
Fur thin cover\forelimb Right				1			1	1	1	
Fur thin cover\lumber								1	1	1
Fur wet\mouth					1					
Fur wet\ventral cervical					1					
Hunched posture									1	
Lying on side				1						
Material dry brown Moderate suspected									3	
Material dry brown										

Sex	Male					Female				
Group	1	2	3	4	5	1	2	3	4	5
No. of animals per group	3	3	3	3	3	3	3	3	3	3
Route of administration	sc				iv	sc				iv
Dose (mg/kg)	0	0.075	0.1	0.166	0.1	0	0.075	0.1	0.166	0.1
moderate					3				1	
Material foamy brown moderate				1						
Material foamy clear Moderate			1						1	
Material foamy clear Moderate suspected									2	
Material foamy particle brown moderate					1			2		1
Material foamy particle brown slight			1	1						
Material foamy white Moderate				1				1	1	
Material foamy white slight								1	2	
Material foamy white Slight suspected									3	
Material liquid black severe suspected					2					
Material liquid brown moderate			1	1	2			1	1	1
Material liquid brown severe				1	2			1	1	
Material liquid brown slight					1				2	
Material liquid clear slight					1					
Material liquid particle black severe suspected					1					
Material liquid particle brown moderate			1		1			1	1	
Material liquid particle brown severe			2		1			1		
Material liquid particle white sever			1							
Material liquid red moderate									1	
Material liquid red Slight			1	1	2				1	
Material liquid yellow										

Sex	Male					Female				
Group	1	2	3	4	5	1	2	3	4	5
No. of animals per group	3	3	3	3	3	3	3	3	3	3
Route of administration	sc				iv	sc				iv
Dose (mg/kg)	0	0.075	0.1	0.166	0.1	0	0.075	0.1	0.166	0.1
moderate									1	
Material liquid red Moderate suspected									1	3
Material mucoid brown moderate									1	
Material mucoid red slight								1	1	
Material mucoid clear slight suspected					3					
Material particle brown moderate									1	
Material mucoid Particle brown suspected										3
Material mucoid particle brown severe									1	
Material mucoid particle red slight					1					
Material mucoid red moderate					1					
Material mucoid red slight			1							
Mouth discharge liquid Red				1						
Muscle tone decreased									1	
Post puncture swelling slight\inguinal left							1	1	1	
Post puncture swelling slight\inguinal right							1	1	1	
Reduced appetite			1		3	1	3	2	3	3
Salivation moderate			1		1				1	2
Salivation\mouth					1					1
Salivation severe			1		2					2
Salivation slight					1		1		1	2
Skin blue\abdominal					2					
Skin blue\hindlimb right	1		2	2	1					
Skin blue\inguinal left		1		2	2		1		1	
Skin blue\inguinal right									1	
Skin blue\priobital left										
Skin blue\priobital right					1			1		
Skin brown\inguinal										

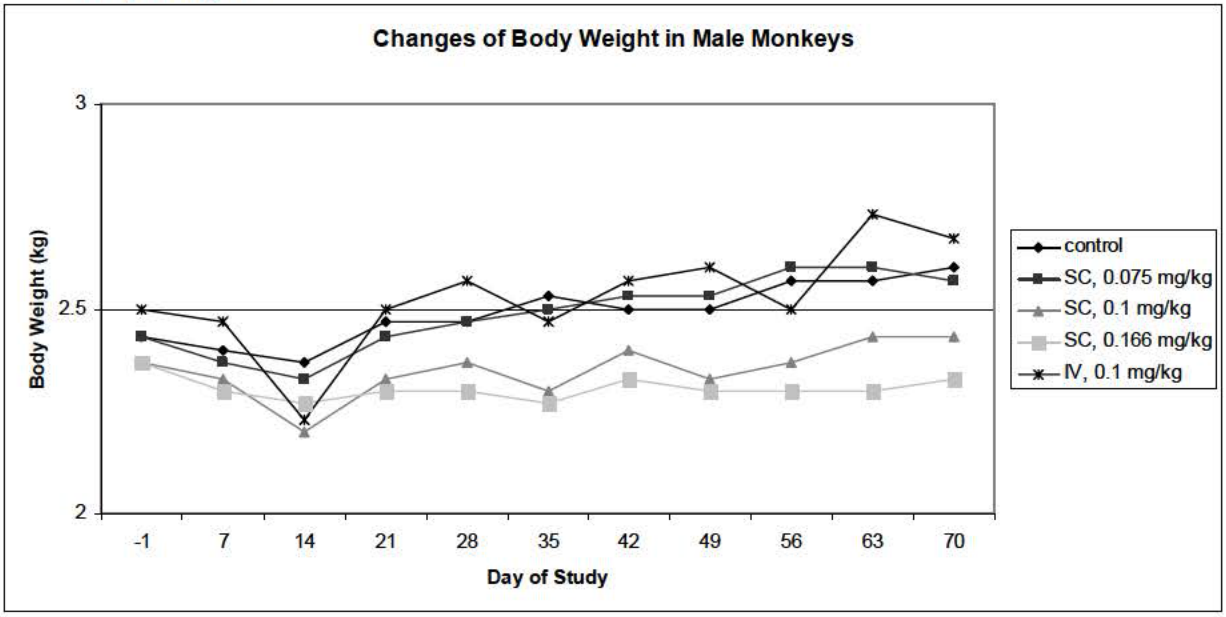
Sex	Male					Female				
Group	1	2	3	4	5	1	2	3	4	5
No. of animals per group	3	3	3	3	3	3	3	3	3	3
Route of administration	sc				iv	sc				iv
Dose (mg/kg)	0	0.075	0.1	0.166	0.1	0	0.075	0.1	0.166	0.1
right			1							
Skin brown\periorbital left				1						
Skin dry\dorsal Thoracic					1					
Skin dry\periorbital left									1	
Skin dry tail									2	2
Skin lesion slight\periorbital right			1	1						
Skin lesion moderat\tail									1	
Skin lesion slight\forepaw left										1
Skin lesion slight\hindlimb right								1		
Skin lesion slight\tail			1	1			1		1	
Skin lesion w/discharge slight\cranium					1					
Skin pale\buccal mucosa				1					1	
Skin pallor				1						
Skin red\hindlimb left					3	1				3
Skin red\hindlimb right			1		3					3
Skin red\mouth		1		1						
Skin red\muzzle		1								
Skin scab\cranium				1	1					
Skin scab\forepaw left										1
Skin scab\hindlimb Right										2
Skin scab\inguinal right										2
Skin scab\urogenital					1					
Skin yellow\hindlimb Right					1					
Swollen slight\hindlimb right										1
Swollen slight\muzzle										1
Swollen slight\periorbital left			1	1						
Swollen slight\periorbital right			1	1						
Thin		1	2	1	2	1		2	2	1

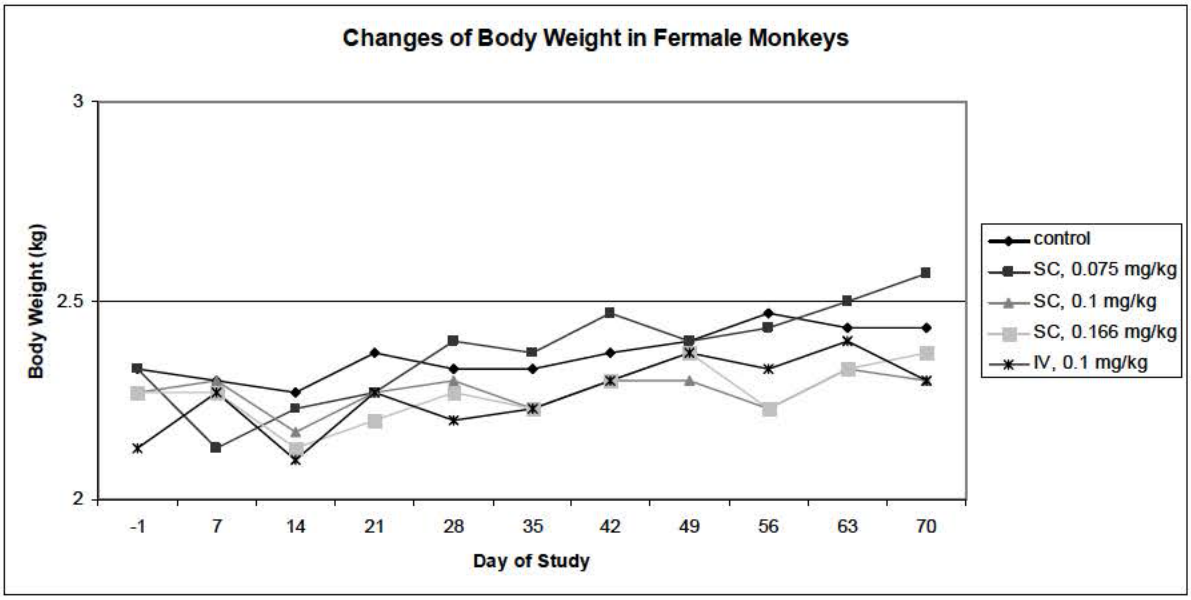
Sex	Male					Female				
Group	1	2	3	4	5	1	2	3	4	5
No. of animals per group	3	3	3	3	3	3	3	3	3	3
Route of administration	sc				iv	sc				iv
Dose (mg/kg)	0	0.075	0.1	0.166	0.1	0	0.075	0.1	0.166	0.1
Vagina discharge liquid clear	-	-	-	-	-		2	1	1	
Vaginal discharge liquid red	-	-	-	-	-		1	2	1	1
Vagina discharge mucoid red	-	-	-	-	-			2	2	1
Vagina discharge mucoid yellow	-	-	-	-	-				1	
Vomitus foamy brown moderate					1					
Vomitus foamy clear Moderate			1							
Vomitus liquid brown moderate				1					1	
Vomitus liquid brown slight					1				1	
Vomitus liquid particle brown moderate				1						
Vomitus liquid particle brown severe					1					
Vomitus liquid yellow moderate									1	
Vomitus liquid yellow Severe					1					
Vomitus foamy particle brown and white mixed moderate									1	
Weak				1						
Found dead				1					1	

Injection site evaluation: a higher incidence of occurrence of erythema and edema in Group 5 (IV), comparing to control and sc treatment groups. The erythema and edema ranged from slight (barely perceptible) to well defined (scores of 1 to 2).

Neurological assessment: unremarkable

Body weights:





Summary: Mean body weights of males at 0.1 and 0.166 mg/kg (SC administration) were lower over the treatment period comparing to the control and LD groups with subcutaneous administration and the group at 0.1 mg/kg with intravenous administration. Body weights of females given bortezomib remained comparable to those of the control group.

Food consumption: No data presented

Ophthalmoscopy: unremarkable

EKG: unremarkable

Hematology:
Early death:
#401: no diagnostic blood samples were withdrawn
#453: Increased total white blood cell counts primarily attributable to an increase in neutrophils. The changes were particularly evident on day 67 (WBC: ↑190% comparing to pretreatment, ↑242% comparing to control on day 77; NEUT: ↑190% comparing to pretreatment, ↑348% comparing to control on day 77)

Index	% deviation compared to control group												
Male													
Route	SC										IV		
Dose	0.075 mg/kg			0.1 mg/kg			0.166 mg/kg*				0.1 mg/kg		
Day of study	14	35	77	14	35	77	11	32	53	81	14	35	77
WBC						-25			-27	6			17
Neutrophils	16	4	-34	6	30	4	-6	-28	-34	54	168	84	76
Monocytes	48	17	88	132	70	101	12	17	20	-44	387	115	74
LUC	84	33		179	-22		45	-38	-51	33	80	38	
RBC	-3			-15	-12	-23	-7	4		3	-8	-10	-10
Platelets	-12	-32	-44	-24	-30	-62	-15	-19	24	-27	-16	-12	-40
Reticulocytes	21	-10	7	-22	-38	20		-13	-8	-2		37	-17
APTT		-24	-34		-22	-24		-24	-13	-18		-7	-23
Female													
Route of adm.	SC										IV		
Dose	0.075 mg/kg			0.1 mg/kg			0.166 mg/kg*				0.1 mg/kg		
Day of study	14	35	77	14	35	77	11	32	53	81	14	35	77
WBC	-19	-11	-9	-17	-23		38	38	71	-30	-3	16	7
Neutrophils	-37		10	-45		38	32	109	204	-56	-22	22	46
Monocytes			73			179			232	-38			151
LUC			18	186	50	288	149	55	293	-59	63		
Platelets			-8	-36	-41	-56	-12	-19	-22		-25	-31	-40
Reticulocytes	-17		-29	-3		-23	-7		22	-16	-22	-12	-24
APTT			13	16		10	-8			55	11		10

*values on days 11, 32, 53 are compared to the values in control groups on day 14, 35, 77 respectively
Values on day 81 are compared to the values on day 53 to show the reversibility after 1 week of recovery

Summary:

- The pattern of changes with SC route was similar to that with IV injection.

Clinical chemistry:
Early deaths:
#401: unremarkable
#453: increased serum triglyceride concentrations were seen on Days 11, 32, 53 and 67 (↑154%, 254, 695, 1461% respectively comparing to the pretreatment levels). Marked increases in urea and creatinine (↑381%, 517% respectively comparing to the pretreatment levels) were observed on Day 67.
Scheduled deaths: unremarkable

Urinalysis: no treatment related effect

Gross pathology: unremarkable

Organ weights:

	% deviation compared to control group															
	Absolute (%)								Relative to Body Weight (%)							
Route	SC						IV		SC						IV	
Dose (mg/kg)	0.075		0.1		0.166		0.1		0.075		0.1		0.166		0.1	
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Kidney	17	20	13	31	1	30	24	8	16	19	21	42	7	34	24	16
Liver	7	23	15	17	5	24	20	11	6	21	24	26	11	29	20	19
Pituitary	25	6	1	12	18	-13	28	8	24	4	10	19	24	-11	24	16
Spleen	33	-2	-19	-3	-18	-11	90	-8	30	-5	-9	4	-13	-8	81	-3
Thymus	-26	22	-67	0	-36	-43	-51	-14	-28	21	-63	7	-32	-39	-54	-9
Thyroid	19	11	-37	-9	-39	-40	-34	-11	19	13	-33	-1	-36	-36	-36	-3

Summary: Increased organ weights (both absolute weights and relative to body weights) occurred after treatment in the kidney, liver, pituitary. Decreased organ weights (both absolute weights and relative to body weights) were observed in the spleen (SC only), thymus and thyroid. Changes in organ weights were generally similar with two different administration routes, except that means weight in spleen was higher when the treatment was given by IV injection. Overall, similar patterns were observed after SC or IV administration.

Histopathology: Adequate Battery: yes (x), no ( )
Peer review: yes (x), no ( )

Early death:
#401: hematopoietic hypocellularity of bone marrow
#453: hematopoietic hypocellularity of bone marrow, vascular leukocytosis in the liver and lung

All animals:

Sex	**male**					**female**				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Number of animals per group	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Bone marrow										
Hypocellularity: hematopoietic			1	2	2				1	1
Heart										
Inflammation		2	2	1	3	1	3	2	3	2
Fibrosis										1
Hemorrhage										1
Injection site saphen. LT										
Hemorrhage							-	-	-	2
Inflammation							-	-	-	1
Kidney										
Degeneration/hypertrophy:			1	3	2		2	2	2	1
tubular			1	1	3			2	1	1
Prominent mesangial cells			1		1		1			
Hemorrhage: tubular					1			1		
Eosinophilic droplets: tubular epithelia					1					
Congestion					1		2	1	1	1
Liver			1	1						
Infiltration: mixed cell										
Reactive sinusoidal lining cells			1	2					2	
Lumbar D. root			1			1				
Degeneration: nerve fiber										
Inflammation								1	3	
Lumbar D. root gangl										
Degeneration: nerve fiber				1						
Lung										
Thrombosis				1	1			1	2	
L. node mandibular										
Atrophy/necrosis: lymphoid			1	1	1			1	1	
L. node mesenteric										
Atrophy/necrosis: lymphoid									2	
Nerve peronea;										
Degeneration: nerve fiber			1	1					2	1
Nerve sciatic										
Degeneration: nerve fiber			1							
Nerve sural										

Inflammation				2					3	1
Nerve tibial										
Degeneration: nerve fiber									2	1
Nerve trigeminal										
Degeneration: nerve fiber		1	2	1						1
Pituitary										
Cyst			1							
Skin			1							
Hyperplasia: sebacepus gland								1		
Hyperplasia: epidermal										
Ulceration			1							
Spinal cord cervical										
Degeneration: nerve fiber			1			1			2	
Spinal cord lumbar										
Degeneration: nerve fiber							1		2	
Spinal cord thoracic										
Degeneration: nerve fiber				1	1		1		1	
Spleen		1	1	2	2					
Atrophy/necrosis: lymphoid				1		1			1	
Hyperplasia: lymphoid										
Fibrosis: capsular				1						
Stomach										
Congestion				1						
Thor. D. root										
Degeneration: nerve fiber			1	1	2				2	
Thymus										
Atrophy/necrosis: lymphoid								1		
Thyroid										
Ectasia: follicular										

"-" not examined.

Summary: histopathological evaluation revealed treatment-related effect in the central and peripheral nervous systems, the hematopoietic system, and in the kidneys. Histopathological changes were also seen in the heart, stomach, liver, lung and the injection sites. Overall, there were no toxicologically significant differences in microscopic findings after SC or IV dosing; see shaded columns above, Group 3 (0.1 mg/kg SC) and Group 5 (0.1 mg/kg IV).

Toxicokinetics: The following table is from the application.

Systemic exposure in blood

Occasion	Group	T_{max} h	C_{max} ng/mL	AUC_{0-72h} h.ng/mL
First (Cycle 1 [Day 1])	5M	0.117	154	5039
	5F	0.25	300	4846
	5	0.184	227	4943
First (Cycle 1 [Day 1])	2M	0.117	108	3786
	2F	0.117	108	3646
	2	0.117	108	3716
First (Cycle 1 [Day 1])	3M	0.117	132	4416
	3F	0.184	149	4791
	3	0.117	139	4566
First (Day 1)	4M	0.117	242	6339
	4F	0.25	197	5536
	4	0.117	215	5857
Cycle 2 [Day 32])	5M	0.117	225	7399
	5F	0.167	189	6863
	5	0.117	207	7131
Cycle 2 [Day 32]	2M	0.133	179	6524
	2F	0.117	164	6032
	2	0.125	172	6278
Cycle 2 [Day 32]	3M	0.117	220	6511
	3F	0.117	230	7422
	3	0.117	225	6966
Day 50	4M	0.117	242	6539
	4F	0.117	223	5919
	4	0.117	233	6229
Last (Cycle 4 [Day 74])	5M	0.117	224	6012
	5F	0.117	205	6438
	5	0.117	215	6225
Last (Cycle 4 [Day 74])	2M	0.25	185	6899
	2F	0.133	182	6153
	2	0.192	184	6526
Last (Cycle 4 [Day 74])	3M	0.25	175	5308
	3F	0.25	200	6535
	3	0.25	188	5921
Last (Day 78)	4M	0.25	255	6569
	4F	0.267	194	5781
	4	0.25	230	6175

Calculated dose normalized C_{max} (ng/mL) and AUC_{0-72h} (h.ng/mL)

Dose Group mg/kg)	Day 1 (cycle 1)		Day 32 (Cycle 2)		Day 74 (Last cycle)	
	C_{max}/D	AUC/D	C_{max}/D	AUC/D	C_{max}/D	AUC/D
Group 2(SC, 0.075)	1440	49547	2293	83707	2453	87013
Group 3 (SC, 0.1)	1390	45660	2250	69660	1880	59210
Group 4 (SC, 0.166	1295	35283	1404	37524	1386	37199
Group 5 (IV, 0.1)	2270	49430	2070	71310	2150	62250

Note: The dose normalized C_{max} and AUC_{0-72h} for HD (0.166 mg/kg) were calculated. However, the results were not compared to those from other treatment groups considering the different dose regimen used at HD (0.166 mg/kg).

Summary:

- With subcutaneous administration, blood C_{max} and AUC_{0-72h} values increased less than dose-proportionally;
- There were generally no sex-related differences in the exposures;
- Observed t_{max} occurred at 0.117 h following IV dosing and 0.117 to 0.25 following SC dosing
- Blood exposures were comparable with IV administration and SC administration at 0.1 mg/kg, with the exception of lower C_{max} in Cycle 1 after SC dosing.

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Systemic exposure of bortezomib in plasma

Occasion	Group	T_{max} h	C_{max} ng/mL	AUC_{0-72h} h.ng/mL
First (Cycle 1 [Day 1])	5M	0.117	47.7	117
	5F	0.25	251	150 (n=2)
	5	0.25	149	131
First (Cycle 1 [Day 1])	2M	0.117	58.0	36.7
	2F	0.117	64.2	Not Calculated (n<2)
	2	0.117	61.1	36.7
First (Cycle 1 [Day 1])	3M	0.117	75.9	57.4
	3F	0.117	102	Not Calculated (n<2)
	3	0.117	86.2	77.5
First (Day 1)	4M	0.117	182	168 (n=2)
	4F	0.25	119	Not Calculated (n<2)
	4	0.117	144	160 (n=3)
Cycle 2 [Day 32])	5M	0.117	110	206
	5F	0.167	68.4	128
	5	0.117	89.3	167
Cycle 2 [Day 32]	2M	0.5	36.2	106 (n=2)
	2F	0.117	81.3	114 (n=2)
	2	0.125	58.8	110
Cycle 2 [Day 32]	3M	0.117	130	174
	3F	0.117	151	306 (n=2)
	3	0.117	141	227
Day 50	4M	0.117	173	223
	4F	0.117	164	186
	4	0.117	168	205
Last (Cycle 4 [Day 74])	5M	0.117	138	147
	5F	0.117	109	134
	5	0.117	124	141
Last (Cycle 4 [Day 74])	2M	0.117	60.9	123
	2F	0.117	79.2	121
	2	0.117	70.1	122
Last (Cycle 4 [Day 74])	3M	0.117	117	200
	3F	0.117	109	222
	3	0.117	113	211
Last (Day 78)	4M	0.25	189	296 (n=2)
	4F	0.267	113	162 (n=2)
	4	0.25	158	229

Calculated dose normalized C_{max} (ng/mL) and AUC_{0-72h} (h.ng/mL)

Dose Group mg/kg)	Day 1 (cycle 1)		Day 32 (Cycle 2)		Day 74 (Last cycle)	
	C_{max}/D	AUC/D	C_{max}/D	AUC/D	C_{max}/D	AUC/D
Group 2(SC, 0.075)	813	493	787	1467	933	1627
Group 3 (SC, 0.1)	860	780	1410	2270	1130	2110
Group 4 (SC, 0.166	867	964	1012	1235	952	1380
Group 5 (IV, 0.1)	1490	1310	890	1670	1240	1410

Note: The dose normalized C_{max} and AUC_{0-72h} for HD (0.166 mg/kg) were calculated. However the results were not compared to those from other treatment groups considering the different dose regimen used at HD (0.166 mg/kg),

Summary:

- With subcutaneous administration, plasma C_{max} and AUC_{0-72h} values increased more than proportionally at dose ≤ 0.1 mg/kg;
- There were drug accumulation when comparing exposures on day 1 and day 32; no accumulation was observed beyond cycle 2 with multiple dosing ;
- There were generally no sex-related differences in blood exposures;
- Observed t_{max} occurred at 0.117 -0.5h following IV or SC dosing;
- Comparing to SC administration, plasma exposures at 0.1 mg/kg were higher (~150%) with IV administration on day 1;
- C_{max} and AUC values were higher in whole blood than in plasma, and the difference was more pronounced for AUC than for C_{max} values

7 Genetic Toxicology: no study submitted with this application

8 Carcinogenicity: no study submitted with this application

9 Reproductive and Developmental Toxicology:

no study submitted with this application

10 Special Toxicology Studies: no study submitted with this application

11 Integrated Summary and Safety Evaluation

Bortezomib is approved in the US and several other countries. The Applicant is seeking approval for the subcutaneous route of administration. This application does not involve any changes in the patient population or dosing regimen. Results of a repeat-dose toxicology/TK study in monkeys have been reviewed. Based on this study, toxicities are comparable after SC or IV administration. The PK is also comparable with the exception of lower C_{max} observed in Cycle 1 after SC dosing as compared to the IV administration (blood or plasma). The significance of the difference in the exposure is unclear as this trend was not evident in other dosing cycles.

There are no nonclinical issues to preclude the approval of this application for SC dosing of bortezomib in the proposed patient population.

12 Appendix/Attachments:

The following table is excerpted from the application

Plasma Exposure (AUC in hr*ng/mL) Comparison of Bortezomib in Monkeys and Humans After Subcutaneous Administration

Species	Dose (mg/m^2)	AUC (hr*ng//mL)	Exposure Ratio
Monkey[a]	1.2	211	N/A
Human[b]	1.3	195	1.08
Human[c]	1.3	155	1.36

AUC = area under the concentration-versus-time curve; N/A = not applicable

a Mean of 3 males and 3 females obtained on Cycle 4, Day 74 (Report 501468, Amendment 1).

b Mean of 10 patients, Study CAN 1004 Section 2.7.2.

c Mean of 17 patients, Study MMY-3021 Section 2.7.2.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEI CHEN
10/03/2011

HALEH SABER
10/05/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21-602 **Applicant:** Millennium **Stamp Date:** March 23, 2011,

Drug Name: bortezomib **NDA/BLA Type:** supplement

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		*Appears acceptable.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		*Appears acceptable
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Same formulation; New route of administration
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	n/a		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	*x		
11	Has the applicant addressed any abuse potential issues in the submission?	n/a		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	n/a		

* Issues generally identified during review.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____yes____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Wei Chen, Ph.D 05/12/2012

Reviewing Pharmacologist Date

Saber Haleh, Ph.D 05/12/2012

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEI CHEN
05/12/2011

HALEH SABER
05/16/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	21602/S-027
Drug Name:	Velcade (Subcutaneous)
Indication(s):	Treatment of patients with multiple myeloma and mantle cell lymphoma
Applicant:	Millennium Pharmaceuticals, Inc
Date(s):	Submission: 3/23/2011
	PDUFA: 1/23/2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V (HFD 711)
Statistical Reviewer:	Qing Xu, Ph.D
Concurring Reviewers:	Mark Rothmann, Ph.D., Statistical Team Leader
	Rajeshwari Sridhara, Ph.D., Director, DBV
Medical Division:	Division of Hematology Products
Clinical Team:	Firoozeh Alvandi, M.D., Clinical Reviewer
	Virginia Kwitkowski, Clinical Team Leader
	Ann T Farrell, M.D, Director
Project Manager:	Amy Baird

Keywords:

Non-inferiority, Kaplan-Meier product limit, log-rank test, hazard ratio, Cox regression

Table of Contents

LIST OF TABLES

LIST OF FIGURES (Optional)

1. EXECUTIVE SUMMARY

Velcade intravenous (IV) injection is currently approved in the US for the treatment of multiple myeloma. The applicant submitted current supplemental NDA (sNDA) 21062/S-027 to support the subcutaneous (SC) route of administration as an alternative to the existing intravenous (IV) administration. This sNDA is comprised of one phase III pivotal study MMY-3021 in subjects with multiple myeloma who had received 1 to 3 prior lines of therapy and had measureable evidence of disease progression since their last previous therapy.

The study MMY-3021 met its primary objective of non-inferiority for the primary efficacy endpoint of overall response rate (ORR) (complete response [CR] + partial response [PR]) after 4 cycles of Velcade for SC route relative to IV route. Non-inferiority for the SC route on ORR would be demonstrated if it is ruled out that the true ORR for the SC route (ORR_SC) is less than 60% of the true ORR for the IV route (ORR_IV). This is accomplished by having the 95% CI for ORR_SC-0.6 ORR_IV rule out all negative values. The ORR was 43% in the SC treatment group compared to 42% in the IV treatment group using ITT population. The 95% CI for the difference of ORR_SC-0.6 ORR_IV was (0.07, 0.279) where the lower bound was above 0 and the p-value for the non-inferiority hypothesis is 0.001, indicating that the primary endpoint satisfied protocol-specified criterion for non-inferiority of efficacy for SC treatment relative to IV treatment. The relative risk was 1.01 with 95% of (0.73, 1.40), excluding the pre-specified non-inferiority margin of 0.6.

2. INTRODUCTION

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2.1 Overview

Velcade is currently approved in the US for the treatment of multiple myeloma and is also indicated for the treatment of mantle cell lymphoma in patients who have received at least 1 prior therapy. Velcade is licensed for administration as a bolus intravenous (IV) injection through a peripheral or central IV line.

This sNDA contains data from one phase III pivotal study MMY-3021. The study MMY-3021 is a randomized, open-label, non-inferiority study that compared the efficacy and safety of Velcade administered by either IV or SC route in 222 subjects with progressive disease after prior systemic therapy for multiple myeloma. Subjects were randomly assigned in a 2:1 ratio and were stratified by the number of lines of prior therapy (1 vs >1) and international staging system (ISS) stage. The study consisted of 3 phases; a screening phase, an open-label treatment phase, and a post-treatment follow-up phase.

The current study was the subject of review by the FDA and the EU Regulatory before initiation of the study. A meeting was held with the Agency on 20 August 2007 to discuss the addition of the SC route of administration to the label. The proposed development plan included 2 protocols to support the new route of administration, a nonrandomized pharmacokinetic/pharmacodynamic study and a randomized non-inferiority study to assess safety and efficacy of SC versus IV. Based on EU regulatory recommendation the sponsor integrated the pharmacokinetic/pharmacodynamic study into the randomized non-inferiority study (MMY-3021)

2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR).The analysis dataset was adequate. The clinical study reports and datasets are located at the following location:
\\CDSESUB1\EVSPROD\NDA021602\021602.ENX

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for both studies as well as the related SAS programs for analysis.

The reviewer was able to perform all analyses using the submitted data. No additional data submission was requested.

3.2 Evaluation of Efficacy

3.2.1 Study Objectives

The primary objective of the study was to compare the overall rate (ORR) (complete response [CR] + PR), after 4 cycles, of SC administration of Velcade with IV administration of Velcade in patients with previously treated multiple myeloma.

The secondary objectives were as follows:

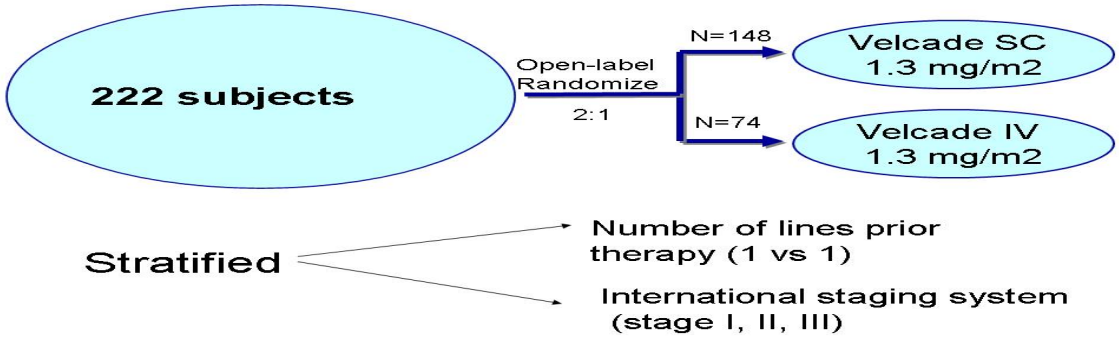
- To determine the CR, near complete response (nCR), and very good partial response (VGPR) rates after 4 cycles of single-agent Velcade, the ORR after 8 cycles including the effect of adding dexamethasone, the duration of response, time to disease progression (TTP), progression-free survival (PFS), 1-year survival, and time to response following VELCADE treatment, administered either SC or IV.

- To evaluate the safety and tolerability of the 2 routes of administration, including the local tolerability of SC administration.
- To describe the plasma pharmacokinetics and pharmacodynamics (via whole blood 20S proteasone inhibition assay) of SC administered Velcade as compared with IV administered Velcade.

3.2.2 Study Design

This was a randomized, open-label, international, multicenter, Phase 3 study that evaluated VELCADE in subjects with multiple myeloma who had received 1 to 3 prior lines of therapy and had measurable evidence of disease progression since their last previous therapy. Subjects were randomly assigned in a 2:1 ratio to receive 1.3 mg/m^2 Velcade either SC or IV and were stratified by the number of lines of prior therapy (1 versus >1) and international staging system (ISS) stage (incorporating beta$_2$-microglobulin and albumin levels; Stages I, II, or III). The planned total sample size was approximately 222 subjects (148 in the SC treatment group vs. 74 in the IV treatment group). The study consisted of 3 phases: a screening phase, an open-label treatment phase, and a post-treatment follow-up phase (Figure 1).

Figure 1 Study Design



During the 21-day screening phase, subject eligibility was confirmed and subjects were then randomly assigned to receive either SC or IV Velcade. During the 24-week open-label treatment phase, subjects were to receive VELCADE on Days 1, 4, 8, and 11 of a 3-week cycle for 8 cycles. If, by investigators assessment, after 4 cycles of therapy, a subject had no change or PR as the best response and had not progressed, dexamethasone could be added to the VELCADE treatment regimen. If added, dexamethasone was to be administered orally at a dose of 20 mg on the day of and the day after Velcade dosing (Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle).

3.2.3 Study Endpoint

Primary Efficacy Endpoint: the primary endpoint was overall response rate (ORR), defined as proportion of subjects who achieved either complete response (CR) or partial response (PR) after 4 cycles (prior to the addition of dexamethasone).

Major Secondary Endpoints:

- CR, nCR and VGPR after 4 cycles; assessment of progressive disease and disease response.
- ORR (CR+PR) after 8 cycles (including the addition of dexamethasone).
- Duration of response, defined as the time from the date of first documentation of a confirmed CR or PR (overall cycles) to the date of first documented PD. Responders without PD were to be censored at the date of the last clinical assessment of response.
- TTP, defined as the time from the date of randomization to the date of first documentation of PD or relapses from CR, whichever occurred earlier. Subjects who had not progressed were to be censored at the date of the last clinical assessment of response.
- PFS, define as the time from the date of randomization to the date of first documented PD, relapse from CR, or death due to any cause, whichever occurred earlier. Subjects who had not progressed and were alive on the cut-off date for analysis were to be censored at the date of the last clinical assessment of response.
- One year survival, defined as the survival rate at 1 year after randomization. Survival was measured from the date of randomization to the date of a subject's death. If a subject was alive or the vital status was unknown, the subject was to be censored at the date that he or she was last known to be alive.
- Time to response.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Table 1 shows the subject enrollment by region and country. Two hundred and twenty-two subjects were enrolled in study MMY-3021 in 10 countries. Subjects were randomly assigned in a 2:1 ratio to receive Velcade as an SC injection (148 subjects) or IV infusion (74 subjects).

Table 1 Subject Enrollment by Region and Country (ITT)

Region Country	IV (N=74) n (%)	SC (N=148) n (%)	Total (N=222) n (%)
Western Europe	30 (41)	43 (29)	73 (33)
France	14 (19)	22 (15)	36 (16)
Belgium	5 (7)	7 (5)	12 (5)
Netherlands	4 (5)	6 (4)	10 (5)
Great Britain	3 (4)	6 (4)	9 (4)
Germany	4 (5)	2 (1)	6 (3)
Eastern Europe	33 (45)	97 (66)	130 (59)
Ukraine	17 (23)	51 (34)	68 (31)
Russia	9 (12)	26 (18)	35 (16)
Poland	7 (9)	20 (14)	27 (12)
Non-Europe	11 (15)	8 (5)	19 (9)
Argentina	8 (11)	5 (3)	13 (6)
India	3 (4)	3 (2)	6 (3)

Data Source: Applicant's clinical statistical report Table 5

Reviewer's Comments:

There is no US site in this study. Imbalances exist for the distribution of enrollment between 2 treatment groups among Western Europe region, Eastern Europe region and Non-Europe region. The majority of subjects (59%) were from Eastern European countries, with 31% of subjects were from Ukraine. There are 73 (33%) subjects that were from Western Europe, with most coming from France (16%)

Table 2 shows subject disposition. Of the 147 treated subjects in the SC treatment group, 81 (55%) subjects completed 8 cycles of treatment, 24 (16%) discontinued due to PD, and 42 (28%) subjects discontinued for reasons other than PD. Of the 74 in the IV treatment group, 50 (68%) subjects completed 8 cycles of treatment, 11 (15%) discontinued due to PD, and 24 (32%) discontinued for reasons other than PD.

Table 2 Subject Disposition

Treatment Status Reason for Treatment Termination	IV (N=74) n (%)	SC (N=148) n (%)	Total (N=222) n (%)
Not treated	0	1 (1)	1 (<1)
Treated	74 (100)	147 (99)	221 (>99)
Cycles 1-8	74 (100)	147 (99)	221 (>99)
Protocol completed	50 (68)	105 (71)	155 (70)
Treatment completed	39 (53)	81 (55)	120 (54)
Treatment discontinued due to pd	11 (15)	24 (16)	35 (16)
Treatment discontinued	24 (32)	42 (28)	66 (30)
Subject choice	2 (3)	4 (3)	6 (3)
Adverse event	18 (24)	31 (21)	49 (22)
--related adverse event	15 (20)	24 (16)	39 (18)
--unrelated adverse event	3 (4)	7 (5)	10 (5)
Death	3 (4)	6 (4)	9 (4)
Other	1 (1)	1 (1)	2 (1)

Data source: Applicant clinical study report table 8

Reviewer's Comments:

More subjects discontinued treatment due to related adverse event in the IV treatment group compared to the SC treatment group.

Demographic and baseline characteristics are summarized for the ITT population in Table 3. In both the SC and IV treatment groups, most subjects were White, median age was 64.5 years and range is from 38 year to 88 year, with 50% of subjects less than 65 years of age, there were more males (64%) versus females (36%) in the IV treatment group. Median baseline KPS score was higher in the IV treatment group compared with the SC treatment group (90% vs 80%), with 51% of subjects in the IV treatment group having a score of 90% or above compared with 40% of subjects in the SC treatment group.

Table 3 Demographic and Baseline Characteristics

	----- IV ----- (N=74)	----- SC ----- (N=148)	--- Total --- (N=222)
Age (years)			
N	74	148	222
Category, n (%)			
<65	37 (50)	74 (50)	111 (50)
≥65	37 (50)	74 (50)	111 (50)
Mean (SD)	64.0 (12.11)	64.3 (8.96)	64.2 (10.09)
Median	64.5	64.5	64.5
Range	(38;86)	(42;88)	(38;88)
Sex, n (%)			
N	74	148	222
Male	47 (64)	74 (50)	121 (55)
Female	27 (36)	74 (50)	101 (45)
Race, n (%)			
N	74	148	222
White	71 (96)	143 (97)	214 (96)
Asian	3 (4)	5 (3)	8 (4)
Baseline KPS (%)			
N	74	148	222
Category, n (%)			
70	12 (16)	32 (22)	44 (20)
80	24 (32)	57 (39)	81 (36)
≥90	38 (51)	59 (40)	97 (44)
Mean (SD)	84.6 (8.94)	82.5 (8.72)	83.2 (8.83)
Median	90.0	80.0	80.0
Range	(70;100)	(70;100)	(70;100)

Data source: Applicant's clinical study report Table 6

Reviewer's Comments:

The sex distribution is imbalanced between 2 treatment groups. There are more males (64%) in the IV treatment group compared to the SC treatment group (50%). There are fewer females (36%) compared to the IV treatment group (50%).

3.2.5 Statistical Methodologies

The applicant defined the following key terms relating to analysis set or measurements or observations:

Intent-to-Treat (ITT) Population: defined as all subjects who are randomized.

Response-Evaluable Population (primary analysis population): defined as all randomized subjects who meet the following criteria:

- Receive at least one dose of study medication;
- Have measurable disease at study entry.

Safety Analysis Set: defined as all subjects who receive at least 1 dose of any study drug. The safety analyses grouping will be according to treatment actually received.

3.2.5.1 Statistical Hypotheses for Trial Objectives

The primary statistical hypothesis is that the SC administered VELCADE is non-inferior to the IV administered VELCADE, as measured by overall response rate (ORR) at the end of 4 cycles. In this study, non-inferiority is defined as retaining 60% of the IV (active control) treatment effect as measured by ORR (a placebo rate of ORR is assumed to be zero).

The non-inferiority hypothesis stated as:
H0: ORRSC-0.60 ORRIV <0 vs H1: ORRSC-0.60 ORRIV≥0 (non-inferiority)

If the non-inferiority of the VELCADE SC administration is claimed, the following superiority hypothesis is to be further tested: there is no difference between the 2 treatment groups with respect to the ORR at the end of 4 cycles.

The superiority hypothesis stated as :
H0: ORRSC- ORRIV <0 vs H1: ORRSC- ORRIV≥0 (superiority)

The property of closed testing procedure ensures that the overall type I error is controlled at level 0.05. Comparisons of all secondary endpoints will be exploratory.

Reviewer's Comments:

On August 16 of 2007, the sponsor met with the Agency to discuss their development plan to extend the route of administration of Velcade to include subcutaneous (SC) injection for the treatment of patients with multiple myeloma. Given that the sponsor's estimation of active control effect size was based on one single study and may not be valid for not accounting for between study variability, the sponsor was recommended to base the sample size calculation on the lower 95% confidence limit of historical response rate. The sponsor was also asked to provide justification for the 60% retention. Per meeting minutes, the sponsor provided details regarding the response rate assumptions and calculations for the proportion retention approach. The sponsor also accepted the FDA's recommendation using lower 95% confidence bound of Velcade IV effect size as the estimate for active control effect.

3.2.5.2 Analysis Methods for Primary Efficacy Endpoint

The 95% CI around ORRSC-0.60 ORRIV will be calculated. In order to declare non-inferiority, the lower bound of this CI need to be greater than or equal to 0. The p-value associated with the non-inferiority hypothesis will be calculated. If non-inferiority is claimed, to further declare superiority, the 95% CI around ORRSC-ORRIV will be calculated. Superiority can be claimed if the lower bound of this CI is greater than or equal to 0. The p-value associated with the superiority hypothesis will be calculated. The CI and p-value calculation will be based on normal approximation.

As a sensitivity analysis, the primary efficacy analysis of the ORR after 4 cycles of Velcade will also be presented for the ITT population

3.2.5.3 Analysis Methods for Secondary Efficacy Endpoints

Secondary efficacy endpoints include CR, nCR, and VGPR rates after 4 cycles of single agent VELCADE, ORR after 8 cycles (including dexamethasone) of treatment, DOR, TTP, PFS, 1-year survival, and TTR. These endpoints are exploratory.

For each response category, the number and percent of subjects will be calculated in each arm. The difference (SC-IV) in the percentage and 95% CI around the difference based on normal approximation will also presented

For ORR and ORR+ MR, the common relative risk of achieving response for the SC vs IV arm is to be calculated. The relative risk estimate is based on Mantel-Haenszel method, stratified by the ISS staging (I, II, and III) and number of prior lines of therapy (1 or more then 1). In addition, p-value (based on normal approximation) for the non-inferiority hypothesis will be provided for ORR and ORR+MR.

The Kaplan-Meier method will be used to estimate the distribution of overall TTP for each treatment group. Hazard ratio and its 95% CI are to be estimated based on a stratified Cox's model with treatment as the explanatory variable. Stratification factors include ISS staging and number of prior lines of therapy. The 1-year survival rate for each treatment group will be presented based on the Kaplan-Meier estimates.

The primary endpoint and secondary response-related endpoints were analyzed using the response-evaluable population as the primary analysis population. Time-to-event endpoints include time to disease progression, 1-year survival, and PFS. They were analyzed using the ITT population as the primary analysis population

Reviewer's comments:

It is not appropriate to use the response-evaluable population as the primary efficacy analysis set for the primary efficacy endpoint; it may not maintain the integrity of the randomizations and against the intent-to-treat principle, as the response-evaluable population is a subset of the ITT population. The ITT population should be the primary basis for making treatment comparison in keeping the randomization principle.

3.2.6 Results and Conclusions

3.2.6.1 Primary Efficacy Analysis Results

The primary efficacy endpoint is ORR (CR+PR) rate after 4 cycles of VELCADE. The ORR in the response-evaluable population was 42% in both SC and IV treatment group. The 95% CI for the difference in ORR_SC-0.6 ORR_IV was (6.1, 27.1) where the lower bound was above 0, and the p-value for the non-inferiority hypothesis is 0.0021, which confirms non-inferiority of SC compared with IV (Table 4).

Table 4 Overall Response Rate during First 4 Cycles (Response-Evaluable Analysis Set)

	IV (N=73)	SC (N=145)
ORR	31 (42%)	61 (42%)
Non-inferiority 95% CI	(6.1, 27.1)	

P-value	0.0021

Reviewer's Comments:

1. *This reviewer replicated the ORR results using the response-evaluable population. The result is consistent with the sponsor's analysis result, which demonstrated non-inferiority of SC compared with IV.*

2. *It is not appropriate to use the response-evaluable population as the primary efficacy analysis set for the primary efficacy endpoint; it is against the intent-to-treat principle, as the response-evaluable population is a subset of the ITT population. The ITT population should be the primary basis for making treatment comparison in keeping the randomization principle. Therefore, this reviewer performed analysis for primary efficacy endpoint based on ITT population. The ORR rate was 43% in SC treatment group compared to 42 % in IV treatment group. The 95% CI for the difference in ORR_SC-0.6 ORR_IV was (7.0, 27.9), where the lower bound was above 0, and the p-value for testing the non-inferiority hypotheses is 0.00106. The relative risk of achieving response for SC versus IV was 1.01 with 95% CI of (0.73, 1.40), which excludes the pre-specified non-inferiority margin of 0.6. However, the study failed to demonstrate superiority of SC treatment to IV treatment.*

3. *The analysis results for the primary efficacy endpoint using ITT population are similar to the analysis results from response evaluable population, which confirms non-inferiority of SC compared with IV (Table 5)*

Table 5 Overall Response Rate during First 4 Cycles (Intent-to-Treat Analysis Set)

	IV (N=74)	SC (N=148)
ORR	32 (42%)	63 (43%)
Non -inferiority 95% CI	(7.0, 27.9)	
P-value	0.00106	
Relative Risk (95% CI)	1.01 (0.73, 1.40)	

3.2.6.2 Secondary and Exploratory Efficacy Analyses

Secondary efficacy endpoints include CR, near complete response (nCR), and very good partial response (VGPR) rates after 4 cycles of single-agent VELCADE, ORR after 8 cycles of treatment, during of response, time to progression (TTP), progression-free survival (PFS), 1-year survival, and time to response.

Reviewer's Comments

In the sponsor's Statistical Analysis Plan, It was stated" Comparisons of all secondary endpoints will be exploratory"; in addition, the study failed to demonstrate the superiority of SC route to

IV route for the primary efficacy analysis. Therefore, all the analyses results for the secondary endpoints should not be included in the labeling.

3.2.6.2.1 CR, nCR, and VGPR Rates after Four Cycles

Table 6 shows the best response rate during the first 4 cycles of treatment using response-evaluable population. After 4 cycle of single-agent Velcade treatment, 9 (6%) of subjects in SC treatment group had CR, compared to 6 (8%) of subjects in IV treatment group; 18 (14%) of subjects in SC treatment group had minor response (MR), compared to10 (14%) of subjects in IV treatment group; 52 (36%) of subjects in SC treatment group had PR, compared to 25 (34%) of subjects in IV treatment group;

The stratified Mantel-Haenszel estimate of the relative risk of achieving ORR+MR for SC vs IV was 0.99 with 95% CI (0.77, 1.26), excluding the pre-specified non-inferiority margin 0.6.

Table 6 Summary of Best Response during First 4 Cycles (Response-Evaluable Population)

Best Response[a]	--- IV --- - N (%) -	--- SC --- - N (%) -	--- Rate Difference -- 95% CI[b]	-- Relative Risk[c] - 95% CI	P-value[d]
Total no. subjects	73	145			
Complete response (CR)	6 (8)	9 (6)	-2.0 (-9.4 , 5.4)		
Partial response (PR)	25 (34)	52 (36)	1.6 (-11.8 , 15.0)		
- near CR	4 (5)	9 (6)	0.7 (-5.8 , 7.3)		
- very good PR	2 (3)	6 (4)	1.4 (-3.6 , 6.4)		
At least very good PR	12 (16)	24 (17)	0.1 (-10.3 , 10.5)		
Overall response rate (CR, PR)	31 (42)	61 (42)	-0.4 (-14.3 , 13.5)	0.99 (0.71,1.37)	0.00201
Minor response (MR)	10 (14)	20 (14)	0.1 (-9.6 , 9.8)		
Overall response + MR	41 (56)	81 (56)	-0.3 (-14.3 , 13.7)	0.99 (0.77,1.26)	0.00004
No change	25 (34)	49 (34)			
Progressive disease	5 (7)	9 (6)			
Not evaluable	2 (3)	6 (4)			

Source data: Applicant's clinical study report Table 30

Reviewer's Comments:

1. *This reviewer replicated the best response rate results using the response-evaluable population. The result is consistent with the sponsor's analysis results.*

2. *This reviewer also did analysis for the best response endpoints using ITT population. After 4 cycle of single-agent Velcade treatment, 11 (7%) of subjects in SC treatment group had CR, compared to 6 (8%) of subjects in IV treatment group; 20 (14%) of subjects in SC treatment group had MR, compared to10 (14%) of subjects in IV treatment group; 52 (35%) of subjects in SC treatment group had PR, compared to 25 (34%) of subjects in IV treatment group. The Mantel-Haenszel estimate of the relative risk of achieving OR+MR for SC vs IV was 1.01 with 95% CI (0.79, 1.29), excluding the pre-specified non-inferiority margin 0.6. The results were similar compared with the results from response-evaluable analysis set, and the non-inferiority objective was also demonstrated. (Table 7)*

Table 7 Reviewer's Summary of Best Response during First 4 Cycles (ITT)

Best Response	IV (N=74)	SC (N=148)	Rate Diff (95% CI)	Relative Risk (95% CI)
CR	6 (8%)	11 (7%)	-0.7% (-8.2, 6.8)	
PR	25 (34%)	52 (35%)	1.4% (-11.9, 14.6)	
MR	10 (14%)	20 (14%)	0.0 (-9.5, 9.5)	
Overall Resp+MR	41 (55%)	83 (56%)	0.7% (-13.2, 14.5)	1.01 (0.79, 1.29)
PD	5 (7%)	9 (6%)		
nCR	4 (5%)	9 (6%)	0.7% (-5.8, 7.1)	
VGPR	2 (3%)	6 (4%)	1.4% (-3.5, 6.2)	

3.2.6.2.2 Overall Response Rate after Eight Cycles

Table 8 shows the ORR during the first 8 cycles of treatment. 76 (52%) of subjects in SC treatment group achieved ORR, compared to 38 (52%) of subjects in IV treatment group. The Mantel-Haenszel estimate of the relative risk of achieving response for SC vs IV is 1.00 with 95% CI (0.77, 1.31)

Table 8 Summary of ORR during First 8 Cycles (Response-Evaluable Analysis Set)

	IV (N=73)	SC (N=145)
ORR	38 (52%)	76 (52%)
Relative Risk (95% CI)	1.00 (0.77, 1.31)	
P-value	0.0001	

Reviewer's Comments:

1. *This reviewer replicated the ORR result during the first 8 cycles using the response-evaluable analysis sets.*

2. *This reviewer also did analysis for the ORR endpoint during the first 8 cycles using ITT population. After 8 cycle of single-agent Velcade treatment, 78 (53%) of subjects in SC treatment group had ORR, compared to 38 (51%) of subjects in IV treatment group. The stratified Mantel-Haenszel estimate of the relative risk of achieving ORR for SC vs IV was 1.02 with 95% CI (0.78, 1.33). The results were similar compared with the results from response-evaluable analysis set (Table 9).*

Table 9 Reviewer's Summary of ORR during First 8 Cycles (ITT)

	IV (N=74)	SC (N=148)
ORR	38 (51%)	78 (53%)
Relative Risk (95% CI)	1.02 (0.78, 1.33)	
P-value	<0.0001	

3.2.6.2.3 Time to Progression (TTP)

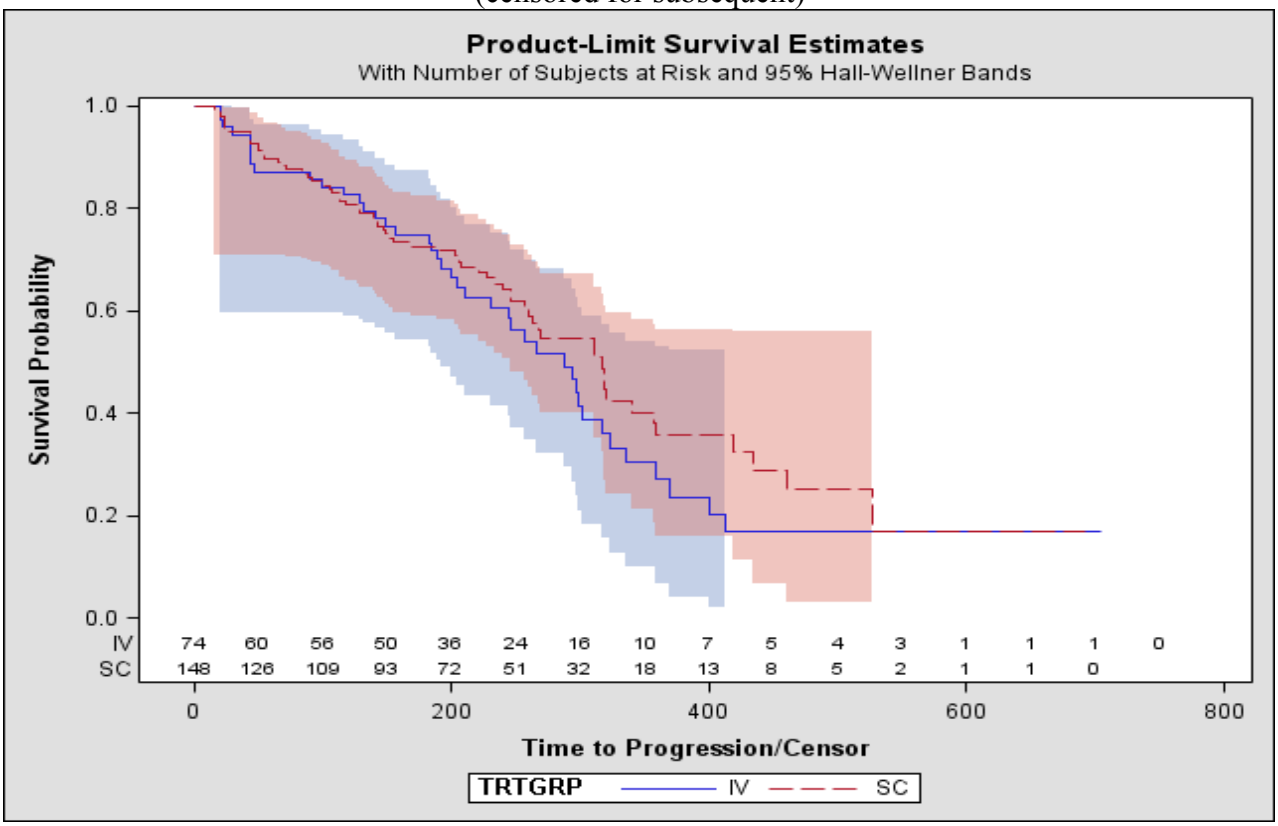
Table 10 shows the sponsor's summary of time to disease progression, censored for subsequent therapy for the ITT population. There were 64 (43.2%) events in the SC treatment group compared to 41 (55.4%) in the IV treatment group. The median PFS was 10.2 month in the SC treatment group compared to 8.0 month in the IV treatment group. The hazard ratio using the stratified Cox proportional hazard model (stratified by ISS staging and number of prior lines) for SC vs IV was 0.839 with 95% CI (0.564, 1.249).

Table 10 Summary of Time to Disease Progression Censored for Subsequent Therapy (ITT)

	IV (N=74)	SC (N=148)
Events	41 (55.4%)	64 (43.2%)
Median (95% CI)	287.0 (231.0, 323.0)	298.0 (259.0, 320.0)
HR (95% CI)	0.839 (0.564, 1.249)	
P-value (adjusted Cox)	0.3867	

Figure 2 shows a Kaplan-Meier plot of time to disease progression (censored for subsequent therapy) using ITT population.

Figure 2 Reviewer's Kaplan-Meier Plot of Time to Disease Progression using ITT Population (censored for subsequent)



*The shading represents Hall-Weller confidence band.

Reviewer's Comments:

1. *Time to progression (TTP) is defined as the duration in days between the date of randomization and the date of first documented evidence of confirmed PD. Those who are lost to follow-up, withdraw consent, or die due to cause other than progressive disease will be censored at their last disease assessment. Those who die of disease progression will be considered as having progressive disease on the date of death. However, deaths prior to detectable progression could present informative censoring for time to progression calculation, and creates a hypothetical endpoint.*

2. *This reviewer also did analysis for the time to disease between two groups using Cox adjusted (adjusting ISS staging and number of prior lines) proportional hazard model, and the results from this reviewer are slightly different from the results from the sponsor. The hazard ratio from this reviewer is 0.827 with 95% CI of (0.558, 1.224) compared to the hazard ratio of 0.839 with 95% CI (0.564, 1.249) from the sponsor.*

3.2.6.2.4 Progression-Free Survival

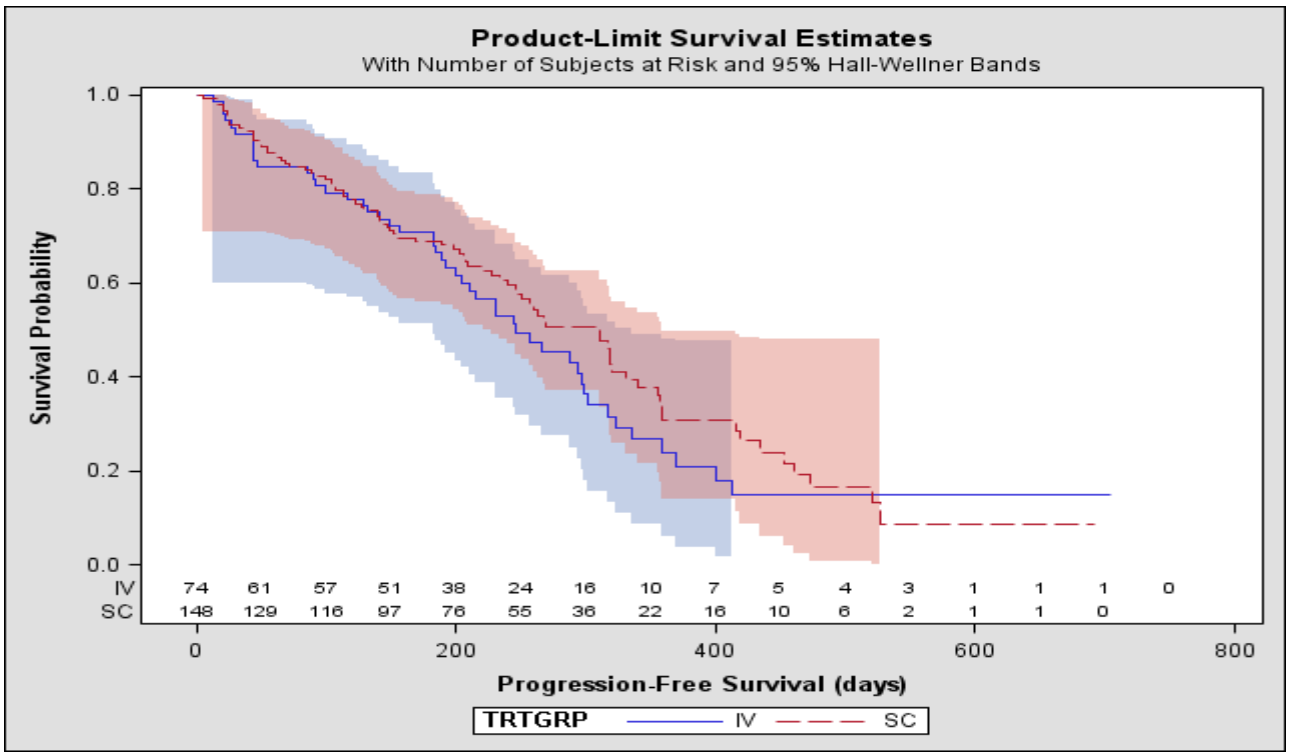
Table 11 shows a sponsor's summary of time to progression-free survival analyses results, censored for subsequent therapy for the ITT population. There were 82 (55.4%) events in the SC treatment group compared to 48 (64.9%) in the IV treatment group. The median PFS was 310 days in the SC treatment group compared to 245 days in the IV treatment group. The hazard ratio using the stratified Cox proportional hazard model (stratified by ISS staging and number of prior lines) for SC vs IV was 0.824 with 95% CI (0.574, 1.183).

Table 11 Summary of Progression-Free Survival Censored for Subsequent Therapy (ITT)

	IV (N=74)	SC (N=148)
Events	48 (64.9%)	82 (55.4%)
Median (95% CI)	245.0 (204.0, 298.0)	310.0 (246.0, 330.0)
HR (95% CI)	0.824 (0.574, 1.183)	
P-value (adjusted Cox)	0.294	

Figure 3 shows a Kaplan-Meier plot of progression free survival (censored for subsequent therapy) using ITT population.

Figure 3 Reviewer's Kaplan-Meier Plot of Progression Free Survival using ITT Population (censored for subsequent)



*The shading represents Hall-Weller confidence band

Reviewer's Comments:

1. *This reviewer also did analysis for the progression-free survival between two groups using Cox adjusted (adjusting ISS staging and number of prior lines) proportional hazard model. The results from this reviewer are slightly different from the results from the sponsor. The hazard ratio from this reviewer is 0.830 with 95% CI of (0.580, 1.186) compared to the hazard ratio of 0.824 with 95% CI (0.574, 1.183) from the sponsor.*

3.2.6.2.6 Overall Survival

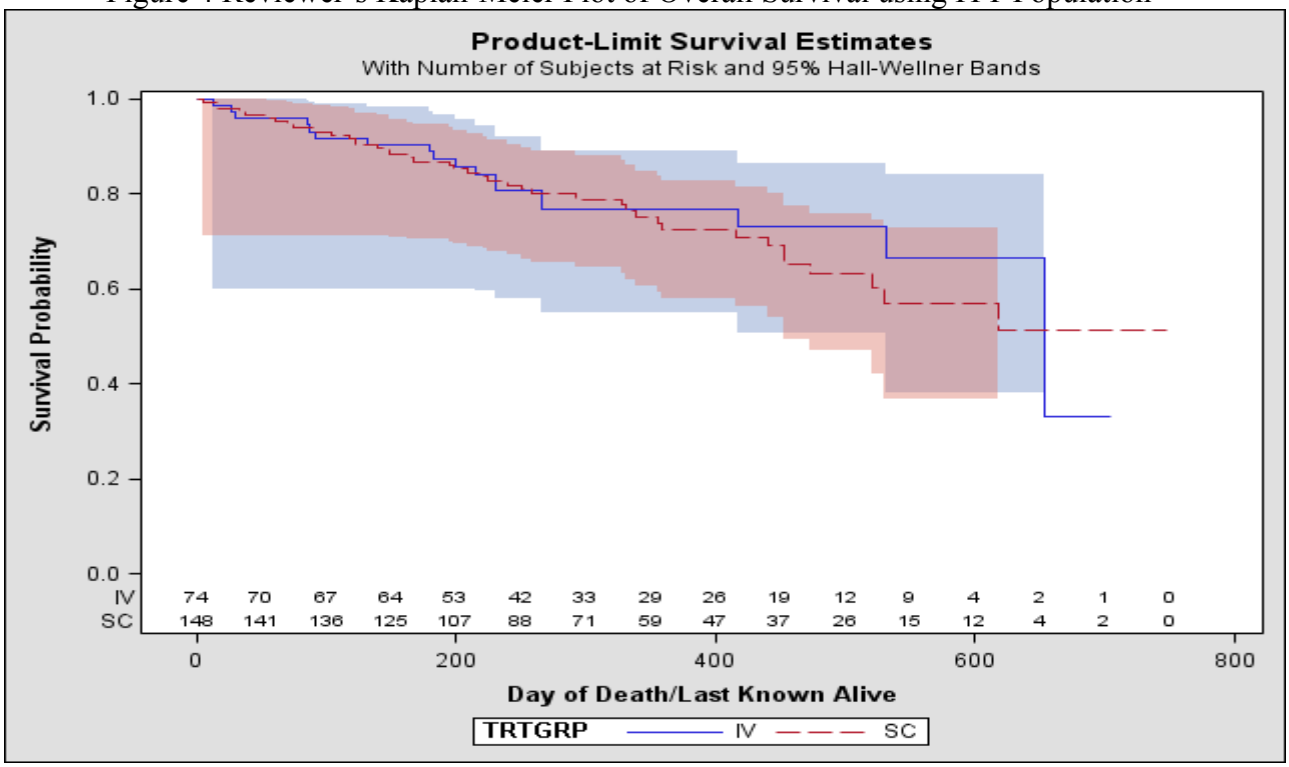
Table 12 shows a sponsor's summary of analysis results for overall survival with one-year survival rate, censored for subsequent therapy for the ITT population. There were 41 (27.7%) deaths in the SC treatment group compared to 18 (24.3%) deaths in the IV treatment group. The one-year survival rate was 72.6% in the SC treatment group with 95% CI of (63.1%, 80.0%), compare to 76.7% in the IV treatment group with 95% CI of (64.1%, 85.4%).

Table 12 Summary of Overall Survival (ITT)

	IV (N=74)	SC (N=148)
Events	18 (24.3%)	41 (27.7%)
1-year survival rate (95% CI)	76.7% (64.1%, 85.4%)	72.6 % (63.1%, 80.0%)
P-value	0.50	

Figure 4 shows a Kaplan-Meier plot of overall survival using ITT population.

Figure 4 Reviewer's Kaplan-Meier Plot of Overall Survival using ITT Population



*The shading represents Hall-Weller confidence band

Reviewer's Comments

The p-value for testing for difference in one year survival of was 0.50, failing to demonstrate a difference in one-year survival rate between the SC and the IV treatment groups.

3.3 Evaluation of Safety

Please refer to the Clinical Review of this application for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, and Geographic Region

4.1.1 Subgroup Analysis by Age

Table 13 presents the summary of best confirmed response during first 4 cycles with age <65 years using response evaluable analysis set.

Table 13 Summary of Best Confirmed Response during First 4 Cycles with Age <65 years (Response Evaluable Analysis Set)

Response	IV (N=36)	SC (N=74)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	16 (44%)	25 (34%)	-10.7% (-30.1%, 8.8%)	0.72 (0.44, 1.17)
CR	4 (11%)	4 (5%)	-5.7% (-17.2%, 5.8%)	
ORR+MR	23 (64%)	37 (50%)	-13.9% (-33.3%, 5.5%)	0.76 (0.54, 1.08)
nCR	2 (6%)	4 (5%)	-0.2% (-9.2%, 8.9%)	

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV

Table 14 presents the summary of best confirmed response during first 4 cycles with age ≥ 65 years using response evaluable analysis set.

Table 14 Summary of Best Confirmed Response during First 4 Cycles with Age >=65 years (Response Evaluable Analysis Set)

Response	IV (N=37)	SC (N=71)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	15 (41%)	36 (51%)	10.2% (-9.5%, 29.8%)	1.26 (0.81, 1.95)
CR	2 (5%)	5 (7%)	1.6 % (-7.8%, 11.0%)	
ORR+MR	18 (49%)	44 (62%)	13.3% (-6.3%, 33.0%)	1.29 (0.89, 1.86)
nCR	2 (5%)	5 (7%)	1.6% (-7.8%, 11.0%)	

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV

4.1.2 Subgroup Analysis by Gender

Table 15 below presents the summary of best confirmed response during first 4 cycles by gender using response evaluable analysis set.

Table 15 Summary of Best Confirmed Response During First 4 Cycles by Gender (Response Evaluable Analysis Set)

Male	IV (N=47)	SC (N=73)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	20 (43%)	28 (38%)	-4.2% (-22.2%, 12.8%)	0.91 (0.57, 1.47)

CR	4 (9%)	5 (7%)	-1.7% (-11.5%, 8.2%)	
ORR+MR	28 (60%)	35 (48%)	-11.6% (-29.7%, 6.5%)	0.80 (0.58, 1.12)
nCR	3 (6%)	4 (5%)	-0.9% (-9.6%, 7.8%)	
Female	IV (N=26)	SC (N=72)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	11 (42%)	33 (46%)	3.5% (-18.7%, 25.7%)	1.01 (0.60, 1.67)
CR	2 (8%)	4 (6%)	-2.1% (-13.7%, 9.4%)	
ORR+MR	13 (50%)	46 (64%)	13.9% (-8.3%, 36.1%)	1.22 (0.83, 1.81)
nCR	1 (4%)	5 (7%)	3.1% (-6.3%, 12.5%)	

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV

4.1.3 Subgroup Analysis by Region

Table 16 below presents the summary of best confirmed response during first 4 cycles with age ≥ 65 years using response evaluable analysis set.

Table 16 Summary of Best Confirmed Response during First 4 Cycles for Western Europe (Response Evaluable Analysis Set)

Response	IV (N=30)	SC (N=41)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	15 (50%)	21 (51%)	1.2% (-22.3%, 24.8%)	1.05 (0.66, 1.66)
CR	2 (7%)	2 (5%)	-1.8% (-12.9%, 9.3%)	
ORR+MR	16 (53%)	27 (66%)	12.5% (10.5%, 35.5%)	1.24 (0.83, 1.86)
nCR	2 (7%)	2 (5%)	-1.8% (-12.9%, 9.3%)	

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV

Table 17 below presents the summary of best confirmed response during first 4 cycles for Eastern Europe using response evaluable analysis set.

Table 17 Summary of Best Confirmed Response during First 4 Cycles for Eastern Europe (Response Evaluable Analysis Set)

Response	IV (N=23)	SC (N=96)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	12 (36%)	39 (41%)	4.3% (-14.9%, 23.4%)	1.13 (0.67, 1.89)
CR	3 (9%)	7 (7%)	-1.8% (-12.9%, 9.3%)	
ORR+MR	19 (58%)	52 (54%)	-3.4% (-23.0%, 16.2%)	0.93 (0.67, 1.30)
nCR	1 (3%)	6 (6%)	3.2% (-4.4%, 10.8%)	

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV

Table 18 presents the summary of best confirmed response during first 4 cycles for Non-Europe using response evaluable analysis set.

Table 18 Summary of Best Confirmed Response during First 4 Cycles for Non-Europe (Response Evaluable Analysis Set)

Response	IV (N=10)	SC (N=8)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	4 (40%)	1 (13%)	-27.5% (-65.5%, 10.5%)	0.69 (0.08, 6.11)
CR	1 (10%)	0	-10.0% (-28.6%, 8.6%)	
ORR+MR	6 (60%)	2 (25%)	-35.0% (-77.7%, 7.7%)	0.48 (0.11, 2.03)
nCR	1 (10%)	1 (13%)	2.5% (-27.0%, 32.0%)	

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV

4.2 Other Special/Subgroup Populations

4.2.1 Subgroup Analysis by ISS Staging (I, II, and III)

Table 19 presents the summary of ORR during first 4 cycles by ISS staging using response evaluable analysis set.

Table 19 Summary of Best Confirmed Response during First 4 Cycles by ISS Staging (Response Evaluable Analysis Set)

Staging I				
	IV (N=20)	SC (N=38)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	7 (35%)	18 (47%)	12.4% (-13.9, 38.6)	1.35 (0.69, 2.64)
Staging II				
	IV (N=29)	SC (N=60)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	14 (48%)	29 (48%)	0.1% (-22.1, 22.2)	0.95 (0.60, 1.50)
Staging III				
	IV (N=24)	SC (N=47)	Rate Different (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	10 (42%)	14 (30%)	-11.9% (-35.5, 11.8)	0.77 (0.38, 1.54)

[a] 95% CI is based on normal approximation with SC rate-IV rate.
[b] relative risk is based on stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV

4.2.2 Subgroup Analysis by Number of Prior Lines of Therapy (1 vs >1)

Table 20 presents the summary of ORR during first 4 cycles by prior lines of therapy using response evaluable analysis set.

Table 20 Summary of Best Confirmed Response during First 4 Cycles by Prior Lines of Therapy (Response Evaluable Analysis Set)

Number of Prior Lines of Therapy:1				
	IV (N=48)	SC (N=88)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	21 (44%)	40 (45%)	1.7% (-15.8%, 19.2%)	1.04 (0.71, 1.54)
Number of Prior Lines of Therapy:>1				
	IV (N=25)	SC (N=57)	Rate Difference (95% CI) [a]	Relative Risk (95% CI) [b]
ORR	10 (40%)	21 (37%)	-3.2% (-26.1%, 19.8%)	0.87 (0.46, 1.62)

Reviewer's Comments

The lower bounds of 95% non-inferiority CI from some of the subgroup analyses are below 0, thus did not meet the non-inferiority criterion (Table 21). However, the statistical power for detecting the same magnitude of treatment effect may be insufficient in those subgroup analyses unless the precision of subgroup estimate has been considered properly in planning the sample size or the variability of the response is sufficiently small in the subgroup. Therefore, we recommend that those subgroup analyses are only exploratory and suggestive, but not conclusive.

Table 21 Subgroup Analysis for the Primary Efficacy Endpoint

	RR (95% CI)	*Lower 95% CI (SC-0.6IV)*	*IV Resp/N*	*SC Resp/N*
Age <65	*0.76 (0.44, 1.17)*	*-0.07*	*16/36*	*25/74*
Non-Europe	*0.69 (0.08, 6.11)*	*-0.41*	*4/10*	*1/8*
# of Prior Lines>1	*0.86 (0.44, 1.67)*	*-0.04*	*10/25*	*20/55*
ISS stage III	*0.77 (0.38, 1.54)*	*-0.12*	*10/24*	*14/47*
Prior transplantation exposure (Y)	*0.85 (0.49, 1.47)*	*-0.108*	*12/20*	*15/30*
Prior thalidomide exposure (Y)	*0.70 (0.41, 1.19)*	*-0.10*	*16/34*	*19/55*
Prior IMID Exposure	*0.81 (0.48, 1.36)*	*-0.05*	*16/38*	*21/60*

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical Issues

This reviewer did not find major statistical issues that would preclude approval of VELCADE for the proposed indication based on review of the pivotal study MMY-3021. However, this reviewer indentified some minor issues may slightly change the efficacy results, but will not alter the conclusion. The issues include:

1. Time to progression (TTP) is defined as the duration in days between the date of randomization and the date of first documented evidence of confirmed PD. Those who are lost to follow-up, withdraw consent, or die due to cause other than progressive disease will be censored at their last disease assessment. Those who die of disease progression will be considered as having progressive disease on the date of death. However, deaths prior to detectable progression could present informative censoring for time to progression calculation, creates a hypothetical endpoint.

2. The sponsor had limited their response rate evaluation in a subset of randomized patients. For keeping the principle of randomization, any efficacy evaluations in a randomized trial should be based upon all randomized patients. This reviewer recommends reporting ITT result for the primary efficacy endpoint.

3. There is no US site that enrolled patients in this study.

4. The lower bounds of 95% non-inferiority CI for some of the subgroup analyses are below 0, thus did not meet the non-inferiority criterion (Table 21). However, the statistical power for detecting the same magnitude of treatment effect may be insufficient in those subgroup analyses unless the precision of subgroup estimate has been considered properly in planning the sample size or the variability of the response is sufficiently small in the subgroup. Therefore, we recommend that those subgroup analyses are only exploratory and suggestive, but not conclusive.

Primary Findings

1. For the primary efficacy endpoint of ORR after 4 cycles of treatment, the response rate was 43% in SC treatment group compared to 42 % in IV treatment group using ITT population. The 95% CI for the difference in the true overall response rate minus 0.6 times the true overall response rate of SC treatment group (ORR_SC-0.6 ORR_IV) was (7.0, 27.9) where the lower bound was above 0 and the p-value for the non-inferiority hypothesis is 0.001, indicating that the primary endpoint satisfied protocol-specified criterion for non-inferiority of efficacy for SC treatment relative to IV treatment.

2. The stratified Mantel-Haenszel estimate of the relative risk of achieving response for SC versus IV was 1.01 with 95% CI of (0.73, 1.40), which excludes the pre-specified non-inferiority margin of 0.6. However, the study failed to demonstrate superiority of SC treatment to IV treatment.

3. The CR rate after 4 cycles of treatment was 6% in the SC treatment group and 8% in the IV treatment group; the nCR rate after 4 cycles of treatment was 6% in the SC treatment group and 5% in the IV treatment group; the VGPR rate after 4 cycles of treatment was 4% in the SC treatment group and 3% in the IV treatment group.

4. The ORR (CR+PR) after 8 cycles of treatment was 52% in both the SC and IV treatment groups for the response-evaluable population. The stratified Mantel-Haenszel estimate of the common relative risk of achieving response for SC versus IV was 1.00 with 95% CI of (0.77, 1.31).

5. The median TTP was 10.4 months in the SC treatment group and 9.4 months in the IV treatment group. The hazard ratio was 0.839 with 95% CI of (0.564, 1.249), and the p-value was 0.386, indicating similar results between the SC and IV groups.

6. The median PFS was 10.2 month in the SC treatment group and 8.0 months in the IV treatment group. The hazard ratio was 0.824 with 95% CI of (0.57, 1.18), and p-value was 0.29 using stratified log-rank test, indicating comparable results between the SC and IV groups.

7. The 1-year survival rate was 72.6% in the SC treatment and 76.7% in the IV arm. The p-value for the difference in 1-year survival rate was 0.5, indicating similar results between the SC and IV arms

5.2 Conclusions and Recommendations

Velcade intravenous (IV) injection is currently approved in the US for the treatment of multiple myeloma. The applicant submitted current supplemental NDA (sNDA) 21062/S-027 to support the subcutaneous (SC) route of administration as an alternative to the existing intravenous (IV) administration. This sNDA is comprised of one phase III pivotal study MMY-3021 in subjects with multiple myeloma who had received 1 to 3 prior lines of therapy and had measureable evidence of disease progression since their last previous therapy.

The study MMY-3021 met its primary objective of non-inferiority for the primary efficacy endpoint of overall response rate (ORR) (complete response [CR] + partial response [PR]) after 4 cycles of Velcade for SC route relative to IV route. Non-inferiority for the SC route on ORR would be demonstrated if it is ruled out that the true ORR for the SC route (ORR_SC) is less

than 60% of the true ORR for the IV route (ORR_IV). This is accomplished by having the 95% CI for ORR_SC-0.6 ORR_IV rule out all negative values. The ORR was 43% in the SC treatment group compared to 42% in the IV treatment group using ITT population. The 95% CI for the difference of ORR_SC-0.6 ORR_IV was (0.07, 0.279) where the lower bound was above 0 and the p-value for the non-inferiority hypothesis is 0.001, indicating that the primary endpoint satisfied protocol-specified criterion for non-inferiority of efficacy for SC treatment relative to IV treatment. The relative risk is 1.01 with 95% of (0.73, 1.40), excluding the pre-specified non-inferiority margin of 0.6.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Qing Xu, Ph.D
Date: December 05, 2011

Concurring Reviewer(s): Rothmann Mark, Ph.D

Statistical Team Leader: Rothmann Mark, Ph.D

Biometrics Division Director: Rajeshwari Sridhara, Ph.D

cc:
Project Manager: Amy Baird
Medical Officer: Firoozeh Alvandi, M.D
Medical Team Leader: Virginia Kwitkowski, RN, MS, ACNP-BC
Medical Division Director: Ann T Farrel, M.D
Primary Statistical Reviewer: Qing Xu, Ph.D
Statistical Team Leader: Rothmann Mark, Ph.D
Biometrics Division Director: Rajeshwari Sridhara, Ph.D
Lillian Patrician

c:\NDA\statreview.doc

CHECK LIST

Number of Pivotal Studies: 1

Protocol Number (s): MMY-3021
Protocol Title : An open-label, randomized study of subcutaneous and intravenous VELCADE in subjects with previously treated multiple myeloma
Phase: 3
Control: Active Control
Blinding: Open-Label
Region(s) (Country): France, Belgium, Netherlands, Great Britain, Germany, Ukraine, Russia, Poland, Argentina, India
Duration: 24 Weeks
Treatment Arms: Velcade
Randomization: Yes
Ratio: 2:1
Stratification Factors: Number of lines prior therapy, international staging system
Primary Endpoint: The primary endpoint was ORR, defined as proportion of subjects who achieved either complete response (CR) or partial response (PR) as defined, after 4 cycles (prior to the addition of dexamethasone).

Primary Analysis Population: response-evaluable population
Statistical Design: Non-Inferiority
If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data? Yes
Margin = 0.6
%Retained = 60%
Adaptive Design: No
Primary Statistical Methodology: The 95% CI around ORRSC-0.60 ORRIV was calculated. In order to declare non-inferiority, the lower bound of this CI need to be grater than or equal to 0.
Interim Analysis: No
Sample Size: 222
Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes

- Were the **Covariates** pre-specified in the protocol? Yes
- Did the Applicant perform **Sensitivity Analyses**? Yes
- Was there a **Multiplicity** involved? No
- **Multiple Secondary Endpoints**: Are they being included in the label? No
- **Were Subgroup Analyses Performed :**Yes
- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report?
- Overall, was the study positive? Yes

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QING XU
12/05/2011

MARK D ROTHMANN
12/06/2011

RAJESHWARI SRIDHARA
12/06/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	21-602/S-27/SDN-278
Submission Date:	23 March 2011
Brand Name:	VELCADE®
Generic Name:	Bortezomib
Formulation:	3.5 mg bortezmib and 35 mg mannitol, USP, in single-dose vials for intravenous injection
OCP Reviewer:	Young Jin Moon, Ph.D.
OCP Team Leader:	Julie M. Bullock, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Hematology Products
Sponsor:	Millennium
Submission Type; Code:	Efficacy supplement; SE2
Dosing regimen:	Approved- 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous injection Proposed- 1.3 mg/m^2 administered as subcutaneous injection
Indication:	Multiple myeloma and mantle cell lymphoma

1 EXECUTIVE SUMMARY

Bortezomib (VELCADE®) is a proteasome inhibitor. Bortezomib, administered as an intravenous (IV) bolus injection, was approved in 2003 in the United States for the treatment of multiple myeloma and later for the treatment of mantle cell lymphoma in patients who have received at least 1 prior therapy.

The current submission is an efficacy supplement for bortezomib which seeks the approval of a subcutaneous (SC) route of administration as an alternative to the existing intravenous one. This sNDA is based on the results of study MMY-3021 which was a randomized, phase 3 study that compared the safety and efficacy of VELCADE administered by either IV or SC route in 222 subjects with progressive disease after prior systemic therapy for multiple myeloma. The primary endpoint, overall response rate was comparable for the SC and IV route of administration. Study MMY-3021 includes a sub-study of 31 subjects to investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of IV and SC VELCADE administration. In addition, a pilot phase 1 study of VELCADE administered by the IV and SC routes (CAN-1004) was conducted. Results of both studies indicated that the PK and PD of bortezomib are comparable with the exception of lower C_{max} observed for SC dosing as compared to the IV administration.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 considers this sNDA acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

Signatures:

Reviewer: Young Jin Moon, Ph.D.	**Team Leader: Julie Bullock, Pharm.D.**
Division of Clinical Pharmacology 5	**Division of Clinical Pharmacology 5**

Cc: DHP: CSO - A Baird; MTL - V Kwitkowski; MO - F Alvandi
DCP-5: Reviewer - Y Moon ; TL – J Bullock
DDD - B Booth ; DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The recommended dosage in relapsed multiple myeloma and mantle cell lymphoma is 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous (IV) injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). The recommended dosage in previously untreated multiple myeloma is 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous (IV) injection in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles. In Cycles 1-4, VELCADE is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, VELCADE is administered once weekly (Days 1, 8, 22 and 29).

The current submission includes a pilot phase 1 PK study (Study CAN-1004) and a PK sub-study from a pivotal phase 3 study (Study MMY-3021). At the 1.3 mg/m^2 dose, bortezomib PK parameters were comparable for the SC injected solution of 1 mg/mL (Study CAN-1004) and 2.5 mg/mL (Study MMY-3021). In both studies bortezomib maximum plasma concentration (C_{max}) was lower for SC administration relative to IV bolus administration. Bortezomib total systemic exposure (AUC) following SC injection was comparable to that of the IV injection. The mean maximum % inhibition of 20S proteasome activity (E_{max}) and the area under the effect time curve for proteasome inhibition (AUE) were comparable between the SC and IV routes.

2 QUESTION BASED REVIEW

Please refer to the original NDA 21-602 (DARRTS communication date: 5/12/03)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the use of SC administered VELCADE as an alternative to IV administration, a randomized, open-label, international, multi-center, phase 3, non-inferiority study was conducted to compare the safety and efficacy of VELCADE administered by either the IV and SC route. The study was performed within the approved indication of relapsed multiple myeloma (N=222) in the approved VELCADE dose and schedule (1.3 mg/m^2 days 1-4-8-11 every 3 weeks) for the treatment duration of 8 cycles. Subjects were randomly assigned in a 2:1 ratio (SC:IV). The new parameter investigated in this study was the novel route of administration and injection concentration (2.5 mg/mL for SC administration). Primary endpoint was overall response rate (ORR) after 4 cycles. The study achieved its primary objective by demonstrating non-inferior ORR after 4 cycles for subjects receiving VELCADE by SC administration compared with those receiving VELCADE by IV administration. The ORR after 4 cycles was 42% in both the SC and IV treatment group. There were less Grade ≥3 adverse events and peripheral neuropathy events reported in the SC treatment group relative to the IV treatment group. The study also assessed the PK and PD of both administration routes of single agent VELCADE in

Cycle 1. Thirty-one subjects were included in these analyses (17 subjects in the SC treatment group and 14 in the IV treatment group).

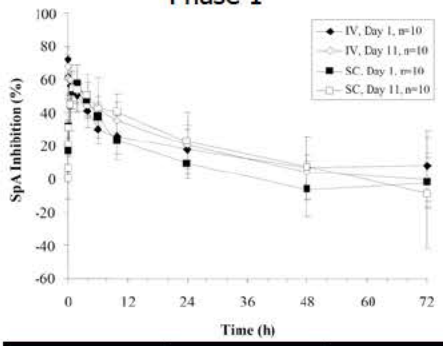
Additional data were provided from Study CAN-1004, a randomized, open-label, multi-center, phase 1 study of VELCADE administered by the IV and SC routes in 24 subjects with progressive disease after prior systemic therapy for multiple myeloma. This study characterized PK, PD, safety and efficacy of subcutaneous VELCADE in the same population used in the phase 3 study. Subjects were randomly assigned in a 1:1 ratio to receive 1.3 mg/m^2 VELCADE either SC or IV on Days 1, 4, 8, and 11 of a 3-week cycle. Bortezomib concentration for the SC injection in this pilot study was 1 mg/mL, which is identical to the currently approved IV injection concentration. Twenty patients were randomized and were evaluable for the PK and PD analyses. The data from this pilot study formed the basis of the design of the Phase 3 MMY-3021 study.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Bortezomib pharmacodynamic parameters (T_{max}, E_{max}, and AUE) were calculated by analysis of the percent inhibition of 20S proteasome activity-time data. Analysis of proteasome inhibition was performed on the change in proteasome activity from baseline to subsequent time points. In both phase 1 (CAN-1004) and phase 3 (MMY-3021) studies the mean maximum proteasome inhibition (E_{max}) and mean area under the effect time curve for proteasome inhibition ($AUE_{0\text{-}72h}$) were comparable following SC or IV administration as shown in Figure 1.

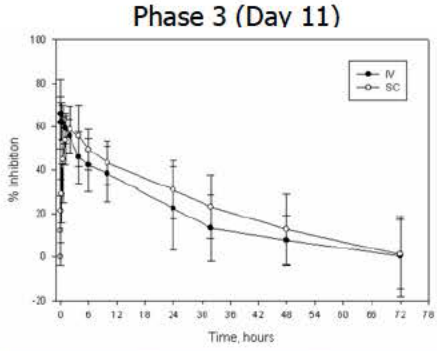
Figure 1. Bortezomib pharmacodynamic profiles and parameters following intravenous or subcutaneous administration of VELCADE 1.3 mg/m^2 on Day 11 of Cycle 1 in Study CAN-1004 (left) and Study MMY-3021 (right).

Phase 1



Parameter (CV%)	IV (N=10)	SC (N=10)
Conc. of Injection Solution	1.0 mg/mL	1.0 mg/mL
E_{max} (%)	68.8 (9.4%)	57.0 (22%)
AUE (%·h)	1283 (46%)	1619 (50%)

Phase 3 (Day 11)



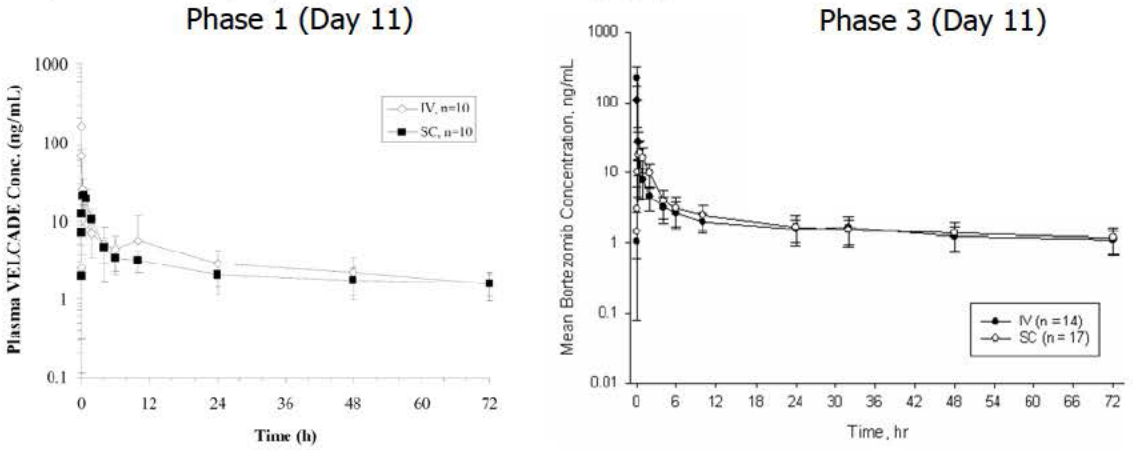
Parameter (CV%)	IV (N=14)	SC (N=17)
Conc. of Injection Solution	1.0 mg/mL	2.5 mg/mL
E_{max} (%)	69 3 (19%)	63.7 (17%)
AUE (%·h)	1383 (55%)	1714 (36%)

2.2.4 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.4.1 What are the single dose and multiple dose PK parameters?

The results of the pharmacokinetics characterization in MMY-3021 were consistent with the results of the phase 1 study CAN-1004. The mean maximum bortezomib concentration (C_{max}) was lower following SC administration compared with IV administration, with median time to reach Cmax occurring within a half hour. The AUC following SC administration was comparable to that of the IV administration in CAN-1004. To reduce the volume of the subcutaneously injected solution, a 2.5 mg/mL concentration was tested in Study MMY-3021. In this study, the AUC following SC injection was equivalent to that of the IV injection with a geometric mean ratio (SC to IV) of 0.992 and 90% CI of 80.18% to 122.80%. The difference in concentration did not affect bortezomib PK and PD parameters following SC VELCADE administration as seen in Table 1.

Figure 2. Mean (SD) plasma bortezomib concentrations and PK parameters following IV or SC administration of VELCADE 1.3 mg/m^2 on Day 11 of Cycle 1 (log-linear scale) in Study CAN-1004 (left) and Study MMY-3021 (right).



Parameter (CV%)	IV (N=10)	SC (N=10)
Conc. of Injection Solution	1.0 mg/mL	1.0 mg/mL
C_{max} (ng/mL)	162 (49%)	22.5 (24%)
AUC (ng · h/mL)	241 (34%)	195 (26%)

Parameter (CV%)	IV (N=14)	SC (N=17)
Conc. of Injection Solution	1.0 mg/mL	2.5 mg/mL
C_{max} (ng/mL)	223 (45%)	20.4 (43%)
AUC (ng · h/mL)	151 (28%)	155 (37%)

Table 1. Summary of Pharmacokinetic and Pharmacodynamic Parameters Following SC Administration at 2.5 and 1.0 mg/mL of VELCADE 1.3 mg/m^2 on Day 11 of Cycle 1 (Studies CAN-1004 and MMY-3021)

Parameter (CV%)	2.5 mg/mL	1.0 mg/mL
C_{max} (ng/mL)	20.4 (43%)	22.5 (24%)
T_{max} (h), (range)	0.5 (0.08-1.00)	0.5 (0.25-1.00)
AUC (ng · h/mL)	155 (37%)	195 (26%)
AUE (% ·h)	1714 (36%)	1619 (50%)
E_{max}(%)	63.7 (17%)	57.0 (22%)

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology studies?

In both studies CAN-1004 and MMY-3021 plasma samples were analyzed for concentrations of bortezomib using a liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method as validated under the method validation report BA (b) (4) All samples were stored in monitored freezers (-70 °C and -80 °C). All samples were within stability documented under BA (b) (4). The data presented on assay accuracy, precision, LLOQ and range/linearity appear acceptable.

3 DETAILED LABELING RECOMMENDATIONS

(b) (4)

Reviewer's note: The sponsor's proposed language is acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YOUNG J MOON
10/19/2011

JULIE M BULLOCK
10/21/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	21602 S-027	**Brand Name**	Velcade
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Bortezomib
Medical Division	OND/OODP/DHP	**Drug Class**	Ubiquitin-proteasome inhibitor
OCP Reviewer	Young-Jin Moon, Ph.D.	**Indication(s)**	-For treatment of patients with multiple myeloma -For treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy
OCP Team Leader	Julie Bullock, Pharm.D.	**Dosage Form**	One single use vial contains 3.5 mg of bortezomib
Pharmacometrics Reviewer	N/A	**Dosing Regimen**	1.3 mg/m^2 twice weekly by IV bolus or SC injection
Date of Submission	23-March-2011	**Route of Administration**	IV, SC
Estimated Due Date of OCP Review		**Sponsor**	Millennium Pharmaceuticals, Inc.
Medical Division Due Date		**Priority Classification**	Standard
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**1**	**1**	**Assay validation report**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

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In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**1**	**1**	**Study CAN-1004**
Phase 3 clinical trial:	**x**	**1**	**1**	**Study MMY-3021**
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**x**	**1**	**1**	**Study CAN-1004**
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
In vitro PD bridge study				
Literature References				
Total Number of Studies	3			

Reviewer's comment:

This is a supplemental NDA which seeks the approval of a subcutaneous route of administration as an alternative to the existing intravenous one. This sNDA is based on the results of Study MMY-3021, a randomized, phase 3 study that compared the safety and efficacy of Velcade administered by either IV or SC route in 222 subjects with progressive disease after prior systemic therapy for multiple myeloma. The primary endpoint was the overall response rate. Study MMY-3021 includes a sub-study of 31 subjects to investigate the PK and PD of IV and SC Velcade administration. Also, a pilot phase 1 study of Velcade administered by the IV and SC routes (Study CAN-1004) was submitted. Study CAN-1004 was a phase 1, randomized PK/PD, safety and efficacy study. Twenty patients were evaluable for the PK and PD analysis. PD parameters (Tmax, Emax and AUE) were calculated by analysis of the percent inhibition of 20S proteasome activity-time data.

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Young-Jin Moon, Ph.D	12-May-11
Reviewing Clinical Pharmacologist	Date
Julie Bullock, Pharm. D.	12-May-11
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YOUNG J MOON
05/12/2011

JULIE M BULLOCK
05/17/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review
Office of Medication Error Prevention and Risk Management

Label, Labeling, Usability and Post marketing Medication Error Review

Date:	January 13, 2012
Reviewer(s):	Terri Wood-Cummings, MD, Division of Medication Error Prevention and Analysis
Team Leader	Zachary Oleszczuk, PharmD Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh, Division of Medication Error Prevention and Analysis
Drug Name(s):	Velcade (Bortezomib) for Injection 3.5 mg/Vial
Application Type/Number:	NDA 021602
Submission Number	S-027
Applicant:	Millennium Pharmaceuticals, Inc.
OSE RCM #:	2007-1769 and 2011-1669

CONTENTS

EXECUTIVE SUMMARY

This review evaluated the Usability studies, labels, and labeling for Velcade for subcutnaeous use. The Usability studies demonstrate that the proposed labels and labeling did not minimize the risk of (1) calculation errors due to the different Velcade concentrations that could lead to overdoses, (2) errors in preperation that can lead to incorrect product concentration and wrong dose, and (3) administering the subcutaneous concentration by intravenous administration or vice versa. Ideally, the product should be developed so that the concentration of the proposed subcutaneous route of administration is the same as the concentration for the the currently marketed intraveouns route of administration because it would eliminate the demonstrated errors in preperation and elimiate the possibilty of administering a different subcutaneous concentration intravensouly or vice versa. However, since the Division of Hematology Products does not expect that inadvertant administration of either concentation to either route of administration would cause clinically significat events, the risk can likely be managed through labels and labeling and education to end users about the difference in concentration follwoing reconsititution.

Additionally, there are already reported cases of fatalities due to overdose of Velcade when the contents of the entire vial are administered. Adding information in the Prescribing Information would be helpful in reminding the practitioners not to adminster the entire vial. However, actually reducing the total drug content per vial would be most effective.

Based on these findings we recomend the following revisions to the labels and labeling to help minmize the risk of wrong calculation errors and wrong dose:

1. We support including intrathercal administration as a contraindication in the Prescirbing Information.
2. Revise the Dosage and Administration of the Prescribing Information to include a sample calculation to assist healthcare practitioners in calculating the dose once Velcade is reconstitute.
3. Revise the Prescribing Information to remove dangerous abbreviations such as “IV” and “SC”.
4. Revise the preparation instructions in the Prescribing Information to instruct practitioners how to use the transferable stickers included with Velcade.
5. Revise the Dosage and Administration section ofr the Prescribing Information to contain a specific referece to “0.9% sodium chloride” (b) (4) .
6. Consider reducing the amount of Velcade that is contained in each vial to minimize the amount of overdose that would occur if an entire vial is given in error.

1 BACKGROUND

Velcade is currently marketed for intravenous administration only. The Applicant proposes to introduce the option of subcutaneous administration (b) (4) . The Applicant is proposing to reconstitute Velcade for subcutaneous administration to a different concentration (2.5 mg/mL) than the currently marketed intravenous administration (1 mg/mL). The Applicant has proposed multiple label and labeling changes to help address confusion that may occur from having two different sets of preparation instructions for different routes of administration. The Usability study attempts to validate these changes.

2 REGULATORY HISTORY

Velcade was approved on May 13, 2003 for intravenous administration only.

On November 11, 2008 the Applicant submitted a supplement for the addition of an alternate drug product manufacturer. This manufacturer, along with an updated Physician Rule Labeling format, was approved in December of 2009.

On September 2, 2010, the Applicant submitted a supplement for the addition of the approved alternate drug product manufacturer BSP Pharmaceuticals in Latina Scalo, Italy on the carton labeling. DMEPA reviewed the carton and container labels in OSE Review #2011-203, dated March 11, 2011 and OSE Review #2011-203-1, dated March 29, 2011. This review considered the medication AERS cases identified up until that point for an open postmarketing review of Velcade (see Appendix C and D for cases considered during those reviews) and made recommendations based on the errors seen at the time of that review. Those recommendations were implemented, and the revised labels and labeling were approved on April 7, 2011.

3 PRODUCT CHARACTERISTICS

Velcade (bortezomib) for Injection is an antineoplastic agent currently approved for intravenous use only. Velcade is indicated for the treatment of patients with multiple myeloma and patients with mantle cell lymphoma who have received at least one prior therapy. The recommended dose of Velcade is 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous injection. Dose adjustment may be used to manage adverse events occurring during treatment. Prior to administration, Velcade needs to be reconstituted with 3.5 mL of 0.9% Sodium Chloride resulting in a final concentration of 1 mg/mL of bortezomib. Velcade is supplied as single use vials containing 3.5 mg of Bortezomib.

The Applicant proposes adding a new subcutaneous route of Velcade administration with the same indications. The recommended starting dose for subcutaneous Velcade is the same 1.3 mg/m^2 administered as a single, subcutaneous injection with dose adjustments as necessary to manage adverse events during treatment. Prior to subcutaneous administration, Velcade needs to be reconstituted with 1.4 mL of 0.9% Sodium Chloride resulting in a final concentration of 2.5 mg/mL of bortezomib. Velcade for subcutaneous injection is supplied as single use vials containing 3.5 mg of Bortezomib.

4 REVIEW METHODS AND MATERIALS

Using Failure Mode and Effects Analysis, the principles of human factors, and post-marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Usability studies (Pre-Summative Usability Test, Summative Usability Test, and Human Factors Engineering Report) submitted October 4, 2011 (no image)
- Container labels, Carton labeling, sticker labeling, and tray lid labeling submitted on October 4, 2011 (See Appendix B)
- Insert Labeling submitted on November 16, 2011 (no image)

Additionally, DMEPA searched the AERS database using the strategies in Table 1 and Table 2.

Table 1: AERS Search Strategy	
Date	July 27, 2009
Drug Names	Verbatim Terms: "Velcade%", "Bortezo%" Tradename: "Velcade" Active Ingredient: "bortezomib"
MedDRA Search Strategy	Higher Level Terms (HLT) "Maladministration", "Medication Errors NEC", "Medication Errors Due to Accidental Exposures", "Medication Monitoring Errors", Preferred Terms (PT): "Overdose", "Accidental Overdose", "Multiple Drug Overdose", "Multiple Drug Overdose Accidental", "Pharmaceutical Product Complaint"

Table 2: AERS Search Strategy	
Date	June 24, 2011
Drug Names	Verbatim Terms: "Velcade%", "Bortezo%" Tradename: "Velcade" Active Ingredient: "bortezomib"
MedDRA Search Strategy	High Level Group Term (HLGT):Medication Errors Preferred Term(PT): Product Quality Issue

5 ANALYSIS OF DATA

5.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE CASES

The AERS database searches resulted in 96 reports. Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. After individual review, 79 reports were not included in the final analysis for the following reasons:

- Reports did not describe a medication error.
- Reports were duplicates of other reports.
- Reports described a medication error not related to the labels or labeling of the product and were not relevant to this review (i.e. wrong patient and accidental exposure).
- Reports described a medication error that DMEPA considered in OSE Review #2011-203, dated March 11, 2009, and DMEPA made recommendations which were approved in April 2011 and were aimed at minimizing these errors (i.e. wrong route of administration and wrong rate of administration).

Following exclusions, we identified 17 Velcade medication error cases for our detailed analysis. All 17 cases described an overdose of Velcade. Appendix E and F provides case details and narratives.

Fourteen of the 17 cases that reported an overdose also reported an actual dose that was administered. Six cases of overdose also reported death as an outcome following the overdose. In all of these cases the only reported medication error was overdose.

The doses reported ranged from 2.6 mg to 2 grams or from 1.6 mg/m^2 to 1.75 mg/m^2 based on body surface area. Seven cases reported that the patient received 3.5 mg. (See Table 3 for complete breakdown of doses).

Table 3: Doses Administered

Reported Dose	Number of Case (n = 17)
Less than 3.5 mg	2
3.5 mg	7
Greater than 3.5 mg	4
Overdose reported but actual dose administered not reported	4

Over one third of the cases that reported an overdose reported that the patient received 3.5 mg or 1 vial of Velcade. Velcade is supplied as a vial that contains 3.5 mg, however this size vial may not be optimal for the dosing recommendations for Velcade. The recommended dose of Velcade is 1.3 mg/m^2. For an average adult patient the typical body surface area would be 2 m^2 or less. Thus, the usual dose of Velcade for an average adult patient would be around 2.6 mg. If an entire vial of Velcade (3.5 mg) was administered in error to an average adult patient who was to receive 2.6 mg, this error would result in the patient receiving 34% more of the intended dose. Reducing the amount of drug contained in each vial of Velcade would not eliminate the risk of overdose but would lessen the amount of the overdose if an entire vial is administered to a patient.

Two of the cases reported patients receiving 3.5 mg because of labeling confusion. Specifically one case stated that the use of the statement "Single dose vial" was confusing, and the nurse interpreted this to mean that one dose was contained in each vial. After reviewing the current labels and labeling DMEPA was unable to locate the statement "single dose vial" on the labels and labeling. There is, however, a statement "Single use vial" that is closely followed by the statement "For Intravenous Use Only". Unfortunately, there is no clear alternative to the statement "Single use vial" at this time. We recognize that this statement may be misinterpreted to mean that an entire vial is to be used at one time. However, we do not have a tested statement to substitute for the current statement. We will continue to monitor for these types of errors through routine postmarketing surveillance. If a validated statement is developed which can replace "Single use vial," we will notify the Division.

The following sections describe our evaluation of the Usability Studies, labels, labeling, and medication errors involving Velcade.

5.2 OBJECTIVE OF THE STUDIES

The Usability Studies were conducted to validate that healthcare professionals can correctly follow packaging and labeling instructions to reconstitute Velcade for intravenous and subcutaneous injection using the proposed labels and labeling. The Velcade subcutaneous route of administration requires a different amount of diluent for reconstitution then the currently marketed intravenous Velcade.

5.2.1 OSE Comments on Objective of the Studies

The Objective of the Study was appropriate.

5.3 DESIGN OF THE STUDY

Two Human Factor studies, a Pre-Summative Usability Test, and a Summative Usability Test were conducted to test the instructions for Velcade preparation found on the container labels and carton labeling and in the preparation and administration sections of the package insert. The Pre-Summative Usability Test consisted of a small group of users who were given a preliminary version of the carton and container labels and labeling and package insert to identify any unexpected use-safety or methodology issues for the Summative Usability test.

After the Pre-Summative Usability Test was completed, revisions were made to the labels and labeling and evaluated in the Summative Test. The Summative Usability Test was conducted using the labels and labeling that are similar to the proposed labels and labeling that have been submitted. Revisions were made to the carton labeling after the Summative Usability Test was completed. These revisions were not validated trough additional summative validation Usability testing. Those changes are discussed in section 5.4.

The test included 45 participants (15 nurses, 15 pharmacist, and 15 pharmacy technicians) who were men and women of various ages, years of experience, and education. Thirty one of the 45 participants had experience reconstituting Velcade. The participants were told, prior to starting the study, that Velcade is now available for subcutaneous administration. The participants were given 4 different Velcade medication orders one at time. Two of the orders were for subcutaneous administration, and two were for intravenous administration. The participants were asked to prepare Velcade for administration based on the order. The setting had all the supplies found at a institution that would administer Velcade. The participants had to select the correct diluent, draw up the correct volume of diluent for reconstitution based on the route of administration, and draw up the correct volume for the final dose of Velcade based on the order. Objective and subjective data were collected. Objective data was collected through direct observation.

The Human Factors Engineering report submitted by the Applicant analyzed the results of the Usability studies in detail.

5.3.1 OSE Comments on the Design of the Study

The design of the Usability studies is reasonable. The studies mimicked real life situations and tested the worst case scenarios where participants did not receive any training prior to completing the assigned tasks and did not mimic situation in which a double check is preformed by a pharmacist or another healthcare provider. Additionally, the participants were acceptable, as they represent the healthcare practitioners who will be preparing Velcade.

The Applicant included practitioners who were both familiar and unfamiliar with Velcade in this study, but did not separate these arms and provided the data in aggregate. This is one area that would have been helpful in teasing out confirmation bias as a source of confusion in the healthcare practitioners familiar with the product versus those unfamiliar with the product. The Applicant could have included an additional arm of healthcare practitioners who are unfamiliar with Velcade in their studies to see if Velcade-naïve practitioners make the same errors as the other groups who are familiar with Velcade. This would have allowed assessment of the impact of the labeling revisions.

5.4 STUDY RESULTS

The Applicant concluded that their study supports the label and labeling revisions effectively communicating the proper means to reconstitute and deliver the drug via subcutaneous or intravenous injections.

The Usability test identified that 14 of the 45 participants (31%) made at least one error during the preparation of Velcade. Some users made multiple errors, thus the total number of errors observed (n=33) is more then the total number of users who made the errors (n=14). The errors include choosing the wrong diluent, using the wrong volume of diluent for reconstitution, and drawing up the wrong volume for the dose ordered on the prescription. Table 4 shows the type of errors observed, how many participants made these errors, and how many times a particular error was made.

Table 4: Use Error Summaries from Summative Usability Test.

Use error description	Number of participants	Number of occurrences	Number of opportunities	Use error rate
Retrieved the incorrect diluent from the pharmacy shelf	1	4	178	2.2%
Drew-up an incorrect diluent volume into the syringe	8	11	178	6.2%
Drew-up an incorrect final volume of reconstituted VELCADE® into the syringe	13	18	178	10.1%

The Applicant acknowledges that errors occurred, however attributed these to human shortcomings rather than shortcomings of the packaging. The Applicant states that none of the participants had difficulty reading or interpreting the directions. However, the Applicant also states that many participants did not read the package insert and made errors during the calculation of the dose. Not reading a package insert is reflective of the real world environment. Thus, we can expect these errors to occur post-approval if the root cause is not minimize or eliminated in its entirety.

5.4.1 OSE Comments on Study Results

We do not agree with the Applicant's assessment that their studies support the label and labeling revisions effectively communicate the instructions for subcutaneous and intravenous administration for the following reasons:

The primary concern is confirmation bias. Fourteen out of 45 (31%) participants made at least one error during preparation of Velcade. The Applicant determined that the errors were due to human short comings. The shortcomings are described as human error in what the applicant considers basic math, using previous knowledge of Velcade and not reading the package insert. These shortcomings are reflective of real world use.

Because practitioners are already familiar with Velcade they may rely on previous knowledge of Velcade during preparation. The Applicant acknowledges the problem associated with confirmation bias in their submission, however they state that the label is not the reason for failure and it is human error that contributed to the errors seen in the study. Because the Applicant did not separate Velcade naive users from Velcade experience users we can not determine if confirmation bias is the only contributing factor to these errors. Because reconstitution and some calculation will be involved in determining the dose of Velcade after reconstitution, all human errors can not be designed out of this product, however, the calculations can be made easier by using the same concentration that the intravenous route of administration uses.

Study participants made errors calculating the diluent needed to prepare Velcade as well as errors calculating the dose of Velcade once reconstituted. The different preparation instructions and different concentrations contributed to these errors. It is unclear if label and labeling revisions will be sufficient to introduce the subcutaneous route of administration into the marketplace without continuing to see this type of postmarketing errors. The communication plan the does not alleviate our concerns of the risk for wrong dose and wrong route of medication errors. The communication plan is a low level strategy that may not reach all healthcare practitioners and will not have a permanent lasting effect on healthcare practitioners after the communication plan has ended. Providing further out reach through the use of articles that reach the targeted groups that prepare this products may also be useful.

The errors occur at the point of product preparation therefore, redesigning the preparation for subcutaneous administration, or removing the intravenous route of administration, may minimize some of the confusion identified with having two sets of preparation instructions and two concentrations for Velcade based on the route of administration. An alternative considered was removal of the intravenous route of administration. However, after communication with OND regarding the necessity for keeping the intravenous route of administration in the package insert we agree that the intravenous route of administration is necessary because it is effective and supported by extensive experience. Replacing the intravenous route of administration with the subcutaneous route of administration is not acceptable because there is not as much postmarketing experience with the subcutaneous route of administration.

Thus, another option to consider for minimizing the risk of miscalculating doses or using the wrong amount of diluent is to require the same preparation instructions for use and concentration as the intravenous route of administration. The package insert states that if injection site reactions occur during subcutaneous administration of the more concentrated Velcade solution, practitioners can consider using a 1 mg/mL concentration for subcutaneous injection. Thus, preparing subcutaneous Velcade in the same manner of intravenous Velcade preparation so that both solutions would result in the same concentration (1 mg/mL) would eliminate one contributing factor to the errors seen in the Usability Studies.

We understand that using the 1 mg/mL concentration for both intravenous and subcutaneous administration would lead to subcutaneous doses greater than 2 mL, the volume limit for subcutaneous administration. However, in those cases a healthcare practitioner could use two different sites of subcutaneous administration for one dose of Velcade. For example, if a patient was prescribed 2.4 mg (2.4 mL) of Velcade the practitioner could inject 1.2 mg (1.2 mL) in two different subcutaneous sites.

Additionally, with only the 1 mg/mL concentration available for intravenous administration DMEPA has not identified any dose calculation errors based on the concentration. DMEPA only identified one calculation error associated with currently marketed Velcade that was previously considered in OSE Review #2011-203, dated March 11, 2011. In that case (ISR #5911538), one physician used the incorrect weight to calculate a patient's body surface area, and that calculation lead to an overdose. This error was not related to labels or labeling. Thus, because healthcare practitioners had difficulty calculating the correct dose in the Usability Studies based on the different concentrations and because we haven't identified any errors related to the current 1 mg/mL concentration on the market we recommend using the 1 mg/mL concentration for the subcutaneous route of administration.

5.5 LABEL AND LABELING

Our review of the Velcade medication errors and product labeling determined that the currently marketed and proposed labels and labeling have implemented revisions to minimize the risk of medication errors identified in our AERS search. However, our review also identified that the amount of drug in each Velcade vial may contribute to the severity of outcomes from overdose cases.

Additionally, after the Usability Studies were completed, the Applicant revised the proposed labels and labeling to the ones submitted for our evaluation. The changes that were implemented included:

- A copy of the reconstitution information (the sticker insert) is now included on the back panel of the carton labeling.
- The warning statement [redacted] (b) (4) on the [redacted] (b) (4) Lid was changed to "Read Reconstitution Information".
- The yellow flag on the principal display panel of the carton labeling was change from [redacted] (b) (4) to " SEE RECONSTITUTION INFORMATION ON BACK".

Although it is unclear whether label and labeling revisions will be adequate to safely implement the subcutaneous route of administration for Velcade, we have identified areas of improvement for the proposed labels and labeling to minimize the risk of medication errors.

5.5.1 OSE Comments on Labels and Labeling

The changes implemented after the Usability Study were not validated by a subsequent Usability Study. Thus, it is unclear what impact these changes would have improving the use of the products or decreasing the type of errors identified in the Usability Study.

Ideally, revising the preparation instructions for subcutaneous administration to be the same as those for intravenous administration, would eliminate the differences in Velcade concentration following reconstitution and therefore eliminate the risk of calculation errors due to the wrong calculation and administering the subcutaneous concentration intravenously or vice versa. However, after discussions with the DHP, we learned that if practitioners administered either concentration (1 mg/mL vs. 2.5 mg/mL) in error, it would be unlikely to result in clinically significant adverse events. Thus, the risks wrong calculation and wrong preparation leading to overdose could be minimized by label and labeling revision, and communication to healthcare practitioners.

The labels and labeling as written do not effectively communicate the different preparation techniques or final concentrations for each route of administration. For example, the Dosage and Administration section of the Highlights of the Prescribing Information does not emphasize the differences in preparation and final concentration for the different routes of administration. Providing this information in the package insert may help practitioners notice that there are two different concentrations so that they are aware of the need to prepare these product differently. Additionally, participants in the Usability Studies had difficulty calculating the dose of Velcade based on the final concentration. Providing a sample calculation in the full prescribing information may help practitioners calculate the correct dose.

The package insert can also provide more specific information when referring to reconstitution directions for Velcade. Currently, the package insert uses [redacted] for the reconstitutions instructions for Velcade. Replacing [redacted] with "0.9% Sodium Chloride", would make the package insert more specific. This is important because one participant picked the wrong diluent 4 different times. The participant was unaware of the multiple types of Sodium Chloride products. Including references to the exact type of diluent may minimize the risk of this error in the future.

[redacted] Although this information was not specifically tested in the Usability Studies, it would be helpful to have the information in the package insert so that healthcare practitioners can understand what to do with the sticker.

The warning statements on the labels and labeling can also be strengthened. The warning statement "SEE RECONSTITUTION INFORMATION ON BACK" in the yellow flag on the principal display panel of the carton labeling is presented in all capital letters and may decrease the readability of this statement. Presenting words and statements in title case (i.e. capital first letter followed by all lower case letters) increases the readability of the words and statements.

We also considered if the route of administration on the container labels and carton labeling of Velcade could be strengthened to minimize the risk of wrong route of administration medication errors. The proposed container labels and carton labeling contain the route of administration [redacted] prominently on principal display panel of the labels and labeling. We considered making this statement stronger by adding the statement "Fatal if give by any other routes of administration" after the current statement, but this statement would not be accurate because if this product was given intramuscular it is unclear if the administration would result in death. Instead, DHP stated that they would be open to include a contraindication in the Prescribing Information for intrathecal administration since intrathecal administration of Velcade would result in death. We support the inclusion of this contraindication in the Prescribing Information.

Additionally, the warning statement "Read Reconstitution Information" on the principal display panel of the [redacted] Lid is generic and may not grab practitioner's attention. The Applicant could develop new language and testing the warning language independently from the other information on the container labels and carton labeling to help strengthen this warning. However, we are not aware of any language that has been developed and validated that would could replace the current statement. Thus, the current warning statement seems reasonable if other label and labeling recommendations are implemented to help minimize the risk of wrong dose errors.

6 CONCLUSIONS

Our review of the Velcade proposed labels, labeling, and Usability Studies determined that the proposed labels and labeling do not adequately address the concern that practitioners will be able to reconstitute and correctly calculate the dose for the subcutaneous route of administration for Velcade. We have provided recommendations in section 7 for the labels and labeling to reduce the risk of preparation errors that could lead to wrong concentration and wrong dose, calculation errors that could lead to wrong dose, and packaging design that could lead to overdose.

We will also develop articles for publication to help raise practitioner awareness of the new route of administration, preparation instructions, and concentration for Velcade.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact the OSE Regulatory Project Manager, Sue Kang, at 301-796-4216.

7 RECOMMENDATIONS

Based on this review and a January 10, 2012, meeting with DHP, DMEPA recommends the following changes to the labels, labeling, and container closure of Velcade.

7.1 COMMENTS TO THE DIVISION

A. Package Insert Labeling

1. The abbreviation "IV" is used by the Applicant throughout the package insert. The abbreviation "IV" appears on the ISMP's List of Error-Prone Abbreviations, Symbols and Dose Designations because it has been misinterpreted as "IU" or "IN". We recommend that the abbreviation "IV" be replaced with the word "intravenous" or "intravenously" where appropriate. DMEPA acknowledges that this abbreviation appears in the labeling of other products. However, in June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone abbreviations in prescribing. As part of this campaign, FDA agreed not to approve such abbreviations in labeling because these abbreviations are carried into the prescribing practice.
2. The (b) (4) is used to indicate 0.9% Sodium Chloride throughout Section 2.8 Reconstitution/Preparation for Intravenous and Subcutaneous Administration in the full prescribing information. We recommend that the (b) (4) be replaced with the term "0.9% Sodium Chloride" in each instance to reinforce the exact diluent needed to reconstitute Velcade. In the Usability study, one person selected the incorrect diluent for all four tasks attempted. We acknowledge that this participant had a knowledge deficit related to diluents in general. However, reinforcing the exact diluent needed for reconstitution for Velcade will help minimize the risk of the wrong diluent being chosen to prepare Velcade.
3. (b) (4) Although this sticker was not specifically tested in the Usability Studies, it does not appear to have contributed to any errors. However, the sticker also appeared to provide limited usefulness. Including information in the package insert of the intent of the sticker and explaining how the sticker can be utilized by healthcare practitioners can could make the sticker more useful.
4. Because practitioners had difficulty with calculating the correct dose of Velcade we recommend revising the Dosage and Administration section of the package insert to include a sample calculation to assist healthcare practitioners in calculating the dose once Velcade is reconstitute. We recommend that following language be incorporated into the Dose and Administration section of the Presribing Information:

   "Calculate the amount of reconstituted Velcade using the following equations:

   - **Intravenous Route of Administration [1 mg/mL concentation]**

     Total dose of Velcade in milligrams = total dose in millilitiers to be administered
     (1 mg/mL)

   - **Subcutaneous Route of Administratin [2.5 mg/mL concentation]**

     Total dose of Velcade in milligrams = total dose in millilieters to be administered
     2.5 mg/mL

5. DMEPA supports including intrathecal adminstration as a contraindication for Velcade.

B. Total Drug Content

We support the inclusion of the statement "The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose" to minimize the risk of administering an entire vial of Velcade. However, we recommend considering decreasing the amount of drug contained in each vial of Velcade in the future development of this product. Velcade is supplied as a vial that contains 3.5 mg of Velcade. The recommended dose of Velcade is 1.3 mg/m^2. For an average adult patient the typical body surface area would be 2 m^2 or less. Thus, the usual dose of Velcade for an average adult patient would be around 2.6 mg. If an entire vial of Velcade (3.5 mg) was administered in error to an average adult patient who was to receive 2.6 mg, this error would result in the patient receiving 34% more of the intended dose. This in fact has occurred in postmarketing resulting in death. Half of the cases describing an overdose stated that 1 vial (3.5 mg) of Velcade was administered. In one case the healthcare practitioner stated that they thought the entire vial of Velcade is to be administered because the vial stated Single Use only. Although reducing the amount of drug contained in each vial of Velcade would not eliminate the risk of overdose, the smaller quantity of drug would lessen the amount of the overdose if an entire vial is administered to a patient and possibly decrease the severity of the overdose.

7.2 COMMENTS TO THE APPLICANT ON CONTAINER LABEL AND CARTON LABELING

Carton and Plastic Tray Lid Labeling

The warning statement "SEE RECONSTITUTION INFORMATION ON BACK" in the yellow flag on the principal display panel of the carton labeling is presented in all capital letters and may decrease the readability of this statement. Presenting words and statements in title case (i.e. capital first letter followed by all lower case letters) increases the readability of the words and statements. We recommend revising this statement to appear as follows:

"See Reconstitution Information on Back"

8 REFERENCES

1. OSE Review #2011-203, Label and Labeling Review for Velcade (Bortezomib) for Injection 3.5mg/vial. Tu, C. March 11, 2011.
2. OSE Review #2011-203-1, Label and Labeling Review for Velcade (Bortezomib) for Injection 3.5mg/vial. Tu, C. March 29, 2011.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS is in compliance with the International Conference on Harmonisation guidance for transmission of individual case safety reports (ICH E2B). Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA). FDA does not require that a causal relationship between a product and event be proven prior to reporting the event to FDA; thus, drug and event causality cannot be assumed when evaluating AERS data. Other limitations of AERS include reporting bias due to media and other factors, underreporting of events and incomplete case data.

4 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix C. AERS Cases Considered in OSE Review #2011-203, dated March 11, 2011

ISR#	Date	Age (years)	Country	Type of Error	Intended Dose or Drug	Dose or Drug Administered	Cause	Outcome
4372102	6-Feb-04	57	CH	Overdose	1.75 mg	3.5 mg	The labeling is confusing	Death
4380171	14-Jun-04	U	US	Wrong Drug	Fludarabine	Velcade	NA	No Adverse Events
4470412	21-May-04	48	US	Wrong Route	NA	2.2 mg	NA	No Adverse Events
4532930	2-Nov-04	U	US	Wrong Rate and Wrong technique (prepared in 100 ml of normal saline)	NA	NA	NA	NA
4533663	27-Sep-04	75	US	Wrong Rate and Wrong technique (prepared in 100 ml of normal saline)	1.3 m2	1.3 m2	NA	No Adverse Events
4612198	23-Aug-04	81	US	Overdose	1 mg	3.5 mg	NA	Death
4614089	1-Mar-05	U	US	Wrong Drug and Wrong Route	NA	Velcade 3 ml	NA	Hospitalization
4616537	17-Dec-04	U	US	Accidental Exposure	NA	NA	NA	Medical Attention
4616996	15-Nov-04	60	US	Overdose (extra dose), Wrong technique (prepared in 100 ml of normal saline), and Wrong rate	2.6 mg once	2.6 mg X2	diluted in bag left unlabeled. Given as hydration therapy	No Adverse Events
4639392	22-Sep-03	69	US	Overdose	1.5 mg	3.5 mg	NA	Prolonged hospitalization Hypotensive, passed out

4692475	13-Apr-05	79	US	Overdose, Wrong Drug, and Wrong Route	Vidiza	Velcade 3.5 mg	Nurse Confused the similar names and picked the wrong one out of pyxis machine	Adverse Events erythyma at injection sites
4692494	13-Jun-05	U	US	Wrong Rate and Wrong technique (prepared in 100 ml of normal saline)	NA	NA	NA	No Adverse event
4693550	1-Jun-05	U	US	Overdose, Wrong technique (prepared in 100 ml of normal saline), and Wrong rate	3.5 mg	3.5 mg	Intentional	No Adverse Events
4693556	16-Dec-04	49	US	Accidental Exposure	NA	NA	NA	Hospitalization recovered
4695250	24-Mar-05	U	US	Wrong Route and Wrong Patient	NA	1.9 mg	NA	No Adverse Event
4881342	1-Jan-05	U	US	Overdose (extra dose)	4 doses/cycle	5 doses	NA	No Adverse Event
4919980	2-May-05	47	JP	Overdose	1.3 m2	1.75 m2 or 1.75 mg	NA	Death
4952195	12-Dec-05	61	FR	Wrong Route	NA	2.3 mg	NA	Death
4991128	14-Mar-06	58	US	Wrong Rate and Wrong technique (prepared in 50 ml of normal saline)	NA		NA	No Adverse Events
4991142	27-Dec-05	63	US	Overdose (extra dose), wrong Rate, and Wrong technique (prepared in 100 ml of normal saline)	NA	2.6 mg X2	NA	NA

5049508	1-Jan-05	U	US	Wrong Rate	NA	NA	NA	No Adverse Events
5074769	3-Apr-06	73	FR	Overdose (extra dose)	2.4 mg x1	2.4 mg x2	NA	Death
5119455	8-Sep-06	50	US	Accidental Exposure	NA	NA	NA	Hospitalization
5188531	13-Jul-06	46	US	Overdose and Wrong Drug	(Avastin) bevacizumab	Velcade bortezomin10 mg	NA	Hospitalization (also wrong dose of oxiplatnin
5228543	9-Mar-06	62	CA	Overdose	NA	6 mg	NA	Death (pnemonia/heatfailure prior to Velcade)
5343439	18-May-07	2	DE	Accidental Exposure	NA	NA	NA	Adverse Events (vomiting abdominal pain
5397127	13-Oct-06	57	US	Overdose	1 mg2	3.5 mg	The statement “Single dose vial” is confusing	Adverse Events (neuropathy and edema)
5455167	4-Sep-07	U	TW	Wrong Rate and Wrong technique (prepared in 100 ml of normal saline)	NA	1.5 mg	NA	Hospitalization
5911538	30-Jul-08	71	US	Overdose	1.3 m2	almost 2x	wrong weight used to calculate body surface area	Prolonged hospitalization Hypotensive and worsening respiratory status
5928314	9-Oct-08	U	IT	Accidental Exposure	NA	NA	NA	Medical Attention
5955997	12-Nov-08	U	US	Overdose	NA	8 mg	NA	Hospitalization (tumor lysis syndrome and neuropathy)
5988512	4-Dec-08	62	JP	Wrong Route	0.175 mg	0.175 mg	NA	Death
6025144	18-Sep-08	71	IT	Wrong Drug and Wrong Route	Methotrexate	2 mg Velcade	NA	Death

6125906	15-Feb-09	73	IE	Wrong Route	2.6 mg	2.6 mg	NA	Death
6249165	23-Apr-09	76	US	Overdose (study)	NA	1.6 mg2	NA	Death

Appendix D. AERS Cases Narratives Considered in OSE 2011-203, dated March 11, 2011

ISR#	Narrative
4372102	Case reference number 104-341-038 is a report from the patient assistance program. This report refers to a female patient aged 57 years (DN). The patient was diagnosed with progressive multiple myeloma (diagnosis date not reported). Prior therapies for disease under study included multiple chemotherapeutic agents (exact therapies not reported), two autologous stem cell transplants and thalidomide. Past medical history included chronic arterial hypertension and diabetes mellitus. Concomitant medications included cefepime, metronidazole, metoprolol, allopurinol, voriconazole, paroxetine and esomeprazole AND methylprednisolone. These medications were administered on 06-Feb-2004. The patient's allergy history was not reported. The patient received VELCADE 3.5 mg (twice the prescribed dose accidentally) via intravenous bolus on 06-Feb-2004 at 15:30. The dose was administered via intravenous bolus over 5 minutes by a registered nurse, not specialized in oncology and in a general internal medicine group. Prior to the medication error, the patient was febrile, with temperature reported between 38 and 38.5 degrees Celsius. The fever was of unknown cause. The patient was also hypercalcemic and thrombocytopenia (values not reported). The patient had no known history of cardiac disease, ischemic cardiac disease or suspicion of amyloidosis. Chest X-ray showed no cardiac hypertrophy and electrocardiogram showed no evidence of hypertension (dates of tests not provided). THE VELCADE TREATMENT WAS ADMINISTERED BY A TRAINED NURSE WITH ADEQUATE QUALIFICATION. THE NURSE MISREAD THE PACKAGE LABEL AND TOOK FOR GRANTED THAT THE CONTENT OF THE ORIGINAL VELCADE VIAL WAS IDENTICAL TO THE PRESCRIBED DOSE. THE MEDICATION ERROR TOOK PLACE IN A GENERAL WARD IN THE CONTEXT OF AN OVERWORKED NURSE TEAM. THE DOSE OF VELCADE GIVEN TO THIS PATIENT WAS NOT LEGIBLE IN THE WRITTEN ORDER. PREVIOUS DOSES OF VELCADE THE PATIENT RECEIVED WERE ADEQUATE, HOWEVER THERE WAS NO SPECIAL PROTOCOL AS WAS REQUIRED AT THE INSTITUTION IN CHEMOTHERAPY. IT HAS BEEN CORRECTED AND VELCADE IS NOW CONDITIONED IN THE PHARMACY AS WITH ANY OTHER CHEMOTHERAPY TREATMENTS. Immediately after the patient received the increased dose of VELCADE, the patient experienced a sharp increase in body temperature to 39.5 degrees Celsius and hypotension, with systemic arterial pressure of 80/40 mmHg at 23:00, which lasted during the night. Despite fluid administration of 1500 mL sodium chloride 0.9%, the patient's events resisted treatment. The investigator reported the cause of the patient's hypotension was not determined (possibly due to sepsis or medication error). The patient also experienced sepsis due to pneumonia, metabolic acidose, renal failure and leukocytes were 3,000/mm3 (reference range was not provided). The patient was admitted to the intensive care unit on (b) (6) at 05:30 with vasoplegic shock, resistant to catecholamine infusion and the patient developed multiple organ failure. On (b) (6) at 16:00, the patient expired due to multiple organ failure secondary to hypotension. AUTOPSY REPORT AND DEATH CERTIFICATE WERE NOT AVAILABLE. The outcomes of the events were fatal. Autopsy results and death certificate were not available, per local law. However, it was reported the death was potentially not due to the disease, but to an external cause, i.e., the medication error. The investigator reported the events as possibly related to treatment with study medication.
4380171	Medication error
4470412	Medication error
4532930	Medication error

4533663	Medication error
4612198	Overdose administration[Overdose] Medication error[Medication error] Haemorrhagic stroke[Haemorrhagic stroke] Aspiration pneumonia[Pneumonia aspiration] Thrombocytopenia[Thrombocytopenia] Case Description: Case reference number 2004-00388 is a spontaneous report referring to a white female aged 81 years (HM), reported by a nurse manager. The patient was diagnosed with multiple myeloma (no date provided). Prior therapies included melphalan, prednisone, cyclophosphamide (Cytoxan) and prednisone, thalidomide, dexamethasone (Decadron), and radiation to her thoracic spine. Past medical history included aspiration pneumonia, cardiac problems (including atrial arrhythmias), lytic bone lesions, gastrointestinal bleeding, and pancytopenia. The patient experienced previous important medical events of thrombocytopenia the week of 12-Jul-2004 and the week of 16-Aug-2004 (see Manufacturer's reports 2004-00469 and 2004-00470, respectively). Concomitant medications were not reported. Allergy history was not provided. The patient received treatment with bortezomib (VELCADE) 1 mg via intravenous bolus from 24-May-2004 until 23-Aug-2004, when she received an accidental overdose of 3.5 mg (Cycle 4, Day 4). On (b) (6), she was hospitalized for accidental overdose and medication error. The hospitalization was prolonged by events of aspiration pneumonia, worsening thrombocytopenia (requiring platelet transfusions), and a hemorrhagic stroke (fatal). On (b) (6) the patient was hospitalized for observation following an accidental overdose and subsequent aspiration pneumonia. Inadvertently, a relatively new nurse administered the entire contents of a 3.5 mg vial instead of the intended 1 mg dosage. This mistake was immediately discovered by the charge nurse. Upon admission, the patient was placed in a monitored unit due to a history of atrial arrhythmias and because of the VELCADE potentially causing cardiac problems. Echocardiogram and electrocardiogram showed no significant changes, and the patient had not displayed any unusual arrhythmias. Laboratory results OBTAINED AT THE ONCOLOGY OFFICE ON 23-AUG-2004 AT 10:15 AM (PRIOR TO THE EVENT) REVEALED A PLATELET COUNT OF 93 X 10^3/UL (150-450 X 10^3/UL) AND A HEMOGLOBIN (HGB) OF 10.0 G/DL (11.0-18.0 G/DL). PRIOR LABORATORY RESULTS OBTAINED ON 16-AUG-2004 AT THE ONCOLOGY OFFICE INCLUDED A PLATELET COUNT OF 112 X 10^3/UL (150-450 X 10^3/UL) AND A HGB OF 10.7 G/DL (11.0-18.0 G/DL); A PLATELET COUNT OF 59 X 10^3/UL WAS NOTED ON 19-AUG-2004. AT 5:43 PM ON (b) (6) LABORATORY RESULTS OBTAINED AT THE HOSPITAL INCLUDED PLATELET COUNT OF 59 K/MMA3 (150-450 K/MM^3), WHITE BLOOD CELLS 11.50 K/MM^3 (4.50-10.50 K/MM^3), GLUCOSE 267 MG/DL (70-110 MG/DL), AND A POTASSIUM OF 2.8 MMOL/L (3.3-5.1 MMOL/L). It was felt the patient possibly could be sent home. She, however, developed worsening thrombocytopenia, as is typical of VELCADE therapy, and was monitored for probable need of continued platelet transfusion. ON (b) (6), LABORATORY RESULTS REVEALED A PLATELET COUNT OF 12 K/MM^3 (150-450 K/MM^3) AND THE PATIENT RECEIVED 1 UNIT OF PLATELETS. The patient was started on prophylactic filgrastrim (Neupogen) because of the possibility of severe neutropenia. ON (b) (4), THE PATIENT'S HEMOGLOBIN (DROPPED TO 7.8 G/DL (11.0-18.0 G/DL); PLATELET COUNT AT THAT TIME WAS REPORTED AS 22 K/MM^3 (150-450 K/MM^3) AND THE WHITE BLOOD CELL COUNT WAS 29.10 K/MM^3 (4.50-10.50 K/MM^3. The patient was found to be occult blood positive and was transferred to the intensive care unit. A pulmonary consultation was called. The patient was started on antibiotics. A CHEST X-RAY PERFORMED ON (b) (6) REVEALED BILATERAL INFILTRATES AS WELL AS VASCULAR CONGESTION THAT COULD NOT BE DIFFERENTIATED FROM OTHER PARENCHYMAL ABNORMALITY. THE PATIENT WAS TRANSFUSED WITH 2 UNITS OF PACKED RED BLOOD CELLS (PRBCS) ON (b) (6). THIS WAS REPORTED AS aspiration pneumonia requiring piperacillin/tazobactam (Zosyn), nebulizer treatments, and steroids. A brief period of hypotension was noted as well. Pindolol (Visken) antibiotic treatment was initiated with support. Gradual improvement was noted, ALTHOUGH FOLLOW-UP CHEST X-RAYS TAKEN THROUGHOUT THE PATIENT'S HOSPITALIZATION SHOWED THE PERSISTENCE OF BILATERAL INFILTRATES. The gastrointestinal bleeding appeared to stabilize with platelet treatment, fresh frozen plasma, and other factors. THE PATIENT RECEIVED ONE UNIT OF PLATELETS AND ONE UNIT OF PRBCS ON (b) (6) ONE UNIT OF PLATELETS ON (b) (6), 2 UNITS OF FRESH FROZEN PLASMA (FFP) AND 2 UNITS OF PRBCS ON (b) (6),

	AND 1 UNIT OF PLATELETS ON [redacted]. ON [redacted] THE WHITE BLOOD CELL COUNT PEAKED AT 55.20 K/MM^3 (4.50-10.50 K/MM^3). THE PATIENT'S HGB ON [redacted] WAS REPORTED AS 11.4 G/DL (12.0-16.0 G/DL) AND PLATELET COUNT WAS 28 K/MM^3 (150-450 K/MM^3). There was a question of heart failure with cardiology and pulmonology monitoring her closely. The patient appeared to improve but then had several episodes of sinus bradycardia. This improved, however, with treatment of her abdominal pain and discomfort. She had problems with diarrhea and Clostridium difficile, requiring metronidazole (Flagyl). Glucose elevation from steroid treatment was also reported WITH THE GLUCOSE NOTED TO BE AS HIGH AS 336 MG/DL (70-110 MG/DL) ON [redacted]. The glucose elevation also improved (GLUCOSE NOTED TO BE 101 MG/DL ON [redacted]). The patient again improved with potential plans for discharge to rehabilitation. The patient developed a sudden onset of some respiratory distress (date not provided). A venogram revealed common femoral vein thrombosis and probable pulmonary emboli; a Greenfield filter was inserted (date not provided). The patient was not able to be treated with anticoagulation therapy due to recent gastrointestinal bleeding. This set off more instability. She experienced additional breathing difficulty and complained of intermittent headaches (date not provided). A COMPUTED TOMOGRAPHY (CT) SCAN PERFORMED ON [redacted] (HEADACHE NOTED AS THE INDICATION) SHOWED STABLE CHRONIC AGE-RELATED CHANGES BUT NO ACUTE ABNORMALITIES. A CT SCAN OF THE ABDOMEN AND PELVIS (ABDOMINAL PAIN NOTED AS THE INDICATION) PERFORMED ON [redacted] SHOWED DIFFUSE INFILTRATING PROCESS WITHIN THE LIVER WHICH MAY REPRESENT METASTATIC DISEASE OR AN UNUSUAL FORM OF NODULAR FATTY INFILTRATION (MRI OF THE LIVER WAS RECOMMENDED FOR FURTHER EVALUATION); BILATERAL PLEURAL EFFUSIONS WITH LOWER LOBE ATELECTASIS; MYELOMA INVOLVEMENT OF THE VERTEBRAL BODIES; 4 CM ABDOMINAL AORTIC ANEURYSM. A GATED CARDIAC VENTRICULOGRAM PERFORMED ON [redacted] SHOWED NORMAL GLOBAL AND REGIONAL BIVENTRICULAR CONTRACTILITY WITH A LEFT VENTRICULAR EJECTION FRACTION OF 60%. It was reported that the patient progressed once again, but on [redacted], she rapidly developed obtundation and drop in mental status. A stat CT scan of the brain PERFORMED ON [redacted] revealed A RATHER LARGE, RELATIVELY ACUTE LEFT MIDDLE CEREBRAL ARTERY AND POSTERIOR WATERSHED TERRITORY INFARCT; THERE WAS A PAUCITY OF MASS EFFECT. THE PATIENT'S PLATELET COUNT ON [redacted] WAS 14 K/MMA3 (150-450 K/MMA3). THE PATIENT RECEIVED ONE UNIT OF PRBCS AND ONE UNIT OF PLATELETS ON [redacted] A FOLLOW-UP CT SCAN OF THE BRAIN PERFORMED ON [redacted] SHOWED A VERY LARGE LEFT CEREBRAL INFARCT, INVOLVING MIDDLE CEREBRAL ARTERY, POSTERIOR WATERSHED AND POSTERIOR CEREBRAL ARTERY TERRITORY, AS WELL AS THE LEFT BASAL GANGLIA (LATERAL STRIATE TERRITORY); THE INFARCT HAD EXTENDED/EVOLVED SINCE [redacted], WITH INCREASED MASS EFFECT, ALTHOUGH NO GROSS HEMORRHAGE WAS NOTED. THE PATIENT RECEIVED 3 UNITS OF FFP ON [redacted], ON [redacted] THE PATIENT RECEIVED A TOTAL OF 2 UNITS OF FFP, 1 UNIT OF PRBCS, AND ONE UNIT OF PLATELETS. ON [redacted], THE PATIENT'S HGB WAS REPORTED AS 6.3 G/DL (12.0-16.0 G/DL), WHITE BLOOD CELLS 9.83 K/MM^3 (4.50-10.50 K/MM^3), AND PLATELET COUNT WAS 11 K/MM^3 (150-450 K/MM^3). SHE RECEIVED ONE UNIT OF PLATELETS ON [redacted], ONE UNIT OF PRBCS ON [redacted], AND ONE UNIT OF FFP ON [redacted]. She also developed possible embolic infarction of the right foot. Given the multiple medical problems and current dibility, including massive cerebrovascular accident and inability to coagulate, the family decided to place her on only comfort care. She subsequently expired at 12:45 on [redacted]. NO AUTOPSY WAS PERFORMED. The immediate cause of death was reported as massive hemorrhagic stroke, but with multiple contributions from chronic dibility due to multiple myeloma, thrombocytopenia, and her chronic debilitated state. The discharge diagnoses reported the following: multiple myeloma, thrombocytopenia due to myeloma, toxicity of chemotherapy, aspiration pneumonia, pulmonary emboli, cerebral emboli with cerebral infarction, coma, gastrointestinal bleeding, respiratory failure, cardiac arrhythmias, metabolic encephalopathy, diarrhea, and renal insufficiency. The physician reported that the patient expired due to medical problems, not all directly related to VELCADE. She was extremely frail and debilitated by her disease, however, the overdose may have in part triggered the thrombocytopenia, which led to the transfusion, prolonged hospitalization, and the

	subsequent chain of events. He believed, however, that she eventually succumbed due to these multiple medical problems and not as a direct result of the VELCADE. Treatment with VELCADE continued unchanged. The outcome for events accidental overdose, aspiration pneumonia, and worsening thrombocytopenia were not reported. The outcome for the event hemorrhagic stroke was reported as fatal. Case Comment:
4614089	Accidental exposure[Medication error] Case Description: Case reference number 2005-00402 is a spontaneous report referring to a female (PN/date of birth not provided), reported by a pharmacist. The oncology diagnosis, patient's medical history, concomitant ,medications, and allergy history were not provided. The patient received bortezomib (VELCADE) 3 ml Intramuscularly on (b) (4) in a medication error. On (b) (4) the patient was in the office to receive another injection (name was unknown) and inadvertently received VELCADE 3 ml intramuscularly (the injection site was unknown). The patient was hospitalized for one day for observation and for precautionary reasons. It was unknown whether the patient experienced any adverse event due to bortezomib injection. Action taken with VELCADE was not applicable since the patient was no longer receiving the drug. The outcome of the event was not reported. Additional information has been requested. Case Comment:
4616537	Hypersensitivity, Accidental exposure, Dermatitis allergic, Skin inflammation
4616996	Overdose
4639392	Medication error[Medication error] Hypotension[Hypotension] Passed out[Loss of consciousness] Nauseous[Nausea] Vomiting[Vomiting] Left bundle branch block[Bundle branch block left] Case Description: Case reference number M03-341-151 is a spontaneous report referring to an African-American male patient aged 69 years (HH) reported by a nurse, and confirmed by a physician. The patient was diagnosed with multiple myeloma approximately January 2000. Prior therapies included cyclophosphamide, etoposide (VP-16), adriamycin, cisplatin and high-dose dexamethasone. Medical history included renal failure, diabetes, heart disease, congestive heart failure, deep vein thrombosis cerebrovascular accident and hypertension. Concomitant medications included dexamethasone (Decadron), heparin, allopurinol, enalapril maleate (Vasotec), furosemide (Lasix), lansoprazole (Prevacid), warfarin (Coumadin), potassium, vicodin (Lortab), insulin and promethazine (Phenergan). The patient's allergy history was not reported. On (b) (6), the patient received dexamethasone (Decadron) 10 mg intravenously and VELCADE 3.5 mg (1.5 mg/m2) via intravenous bolus at 11:15 am. Twenty-five minutes later, the patient stepped into the bathroom, passed out and became unresponsive. In the restroom, the nurse was unable to find a blood pressure (measurement not reported, but baseline prior to treatment blood pressure was 114/62 mmHg, pulse 100). The patient's chest pattern revealed a left bundle branch block, although he had a paced rhythm. Initially he appeared to recover well, but may have stood up too quickly, since he nearly passed out again at 11:40 am. There was a postural drop in blood pressure (UNABLE TO OBTAIN BLOOD PRESSURE WHEN PATIENT WAS UNCONSCIOUS) and the patient experienced dizziness, light-headedness, shock (described as cool, clammy and unresponsive). The patient was easily revived and did not have an irregular pulse. He did not remember any premonitory conditions. He was subsequently transferred to the emergency room and administered oxygen and a liter of normal saline. At 12:18 pm, he became nauseous and vomited. After several hours in the hospital he was alert and oriented, sclerae anicteric, had ptosis in the right eye, some droop in his right mouth upon smiling and a mass on the right side of his face that measured 6.5 x 5.5 cm; these findings were present prior to initiation with VELCADE. The mass greatly decreased in size since treatment and as of (b) (6), he continued to exhibit some facial paralysis. He had no cervical or supraclavicular adenopathy. The patient's breath sounds were again diminished bilaterally, left arm a bit swollen, heart rate regular paced rhythm, and abdomen was obese and nontender. The patient was negative for dehydration, recent blood loss, sepsis, electrolyte or metabolic disturbances, venous thromboembolism, diabetic neuropathy, prior hyperviscosity state or a history with thalidomide. He was negative for adrenal insufficiency, an elevated creatinine level, anemic and recently received diuretic and anti-hypotensive therapy. On (b) (6), creatinine was 1.4 MG/DL (reference range: 0.5-1.2), hemoglobin 7.3 g/dL (reference range: 12-18), hematocrit 21.7% (reference range: 36-54), troponin 0.02 ng/mL

	(normal <0.05) and creatinine kinase MB 1.0 NG/ML (reference range 0.6-6.3). The physician's diagnostic impression was most likely a severe vasovagal or hypotensive episode secondary to velcade. The plan was to observe the patient overnight, transfuse 2 units of red cells since his hemoglobin dropped to 6.3 g/dL (reference range: 12-18 g/dL), with hydration and a follow-up PA and lateral chest X-ray the following morning. It was questionable if the patient's recent deep venous thrombosis was a cause of the hypotension. The patient also recently experienced a cerebrovascular accident with right-sided weakness. The patient was not rechallenged with VELCADE and a discharge summary was not available. THE TREATING PHYSICIAN CONFIRMED THAT THE DOSE OF 1.5 MG/M2 WAS A MEDICATION ERROR. The events were reported as completely resolved (date of resolution was not provided). Manufacturer's Comment: Initial information was received on 11-Nov-2003, and follow-up information was received on 17-Nov-2003 and expedited to the FDA on 25-Nov-2003 and 01-Dec-2003 respectively. Additional follow-up information was received on 26-Jan-2004. Upon further medical review on 15-Apr-2005 it was determined that this additional information required re-submission. Case Comment:
4692475	APPLICATION SITE REACTION ACCIDENTAL EXPOSURE MEDICATION ERROR INJECTION SITE ERYTHEMA
4692494	Medication error
4693550	
4693556	Medication error Accidental exposure Abnormal sensation in the eye
4695250	Medication error
4881342	Accidental overdose
4919980	Aspergillus infection[Cerebral aspergillosis] Pneumonia[Pneumonia] Sepsis[Sepsis] Diffuse alveolar damage[Diffuse alveolar damage] Multi-drug resistant Pseudomonas aeruginosa positive[Pseudomonal bacteraemia] Secondary immunodeficiency[Secondary immunodeficiency] anial infarction[Cerebral infarction] sal pleural effusion[Pleural effusion] Cranial hemorrhage[Cerebral haemorrhage] Neutropenia[Neutropenia] Thromboembolism[Embolism] Respiratory failure[Respiratory failure] Campylobacter jejuni[Campylobacter infection] Fever of 38.2 degrees[Pyrexia] Case Description: Case reference number 2005-01432 is a spontaneous report referring to a female patient aged 47 years (MY), reported by a physician. The patient was diagnosed with multiple myeloma in September 2003. Prior therapies included vincristine, doxorubicin, and dexamethasone (VAD), and autologous stem cell transplant. Her medical history included insulin-dependent diabetes mellitus, Aspergillus pneumonia, hypertension, Aspergillus antigen test positive, and organizing pneumonia. Concomitant medications included insulin. Prior hospitalizations and allergy history were not provided. The patient received bortezomib (VELCADE) 1.75 mg/m^2 via intravenous from [redacted] (Cycle 2, Day 11). On [redacted] (Cycle 1, Day 8), the patient experienced Grade 1 dyspnea. On [redacted], seven days after the last dose for Cycle 1, the patient experienced basal pleural effusion. On [redacted], the day of the last dose for Cycle 2, the patient experienced cough and fever. On [redacted], two days after last dose, the patient experienced pneumonia and Aspergillus infection. On [redacted], eighteen days after last dose, the patient experienced cranial hemorrhage and infarction. On [redacted], twenty-six days after last dose, the patient experienced multi-drug resistant Pseudomonas aeruginosa positive blood culture. In [redacted], the patient experienced neutropenia. The patient expired on [redacted] of pneumonia and Aspergillus infection. The patient went to the hospital to receive treatment with personally imported VELCADE. On [redacted], the patient experienced mild dyspnea, which was treated with oxygen and diuretics and was improved on [redacted]. On [redacted], computed tomography (CT) of chest showed a basal pleural effusion. In the evening of [redacted], after receiving VELCADE, the patient experienced cough and fever in the high 37's degrees Celsius. Chest x-ray was normal. Sputum culture was negative. The

	patient was started on panipenem (Carbenin), which was continued until [redacted], and erythromycin (Erythrocin) was initiated on [redacted]. On [redacted], chest x-ray showed opacity in the right lower lung field. Chest CT revealed lung infiltrates (consolidation), more prominent in the right lower lung field than the right upper. Clindamycin and ciprofloxacin chlorhydrate (Ciproxan) were started. On [redacted], chest CT and chest x-ray showed further progression of infiltrates (consolidation) throughout the lung fields. Beta-D-glucan was 10.5 (reference range and units were of provided). Sputum culture was positive for Staphylococcus aureus. Micafungin sodium (Funguard) was administered and lenograstim Neutrogin) 100 ug was given for neutropenia associated with the terminal multiple myeloma. The patient also received gamma-globulin until [redacted]. On [redacted], chest CT and chest X-ray showed further progression of infiltrates (consolidation) throughout the lung fields. The patient was intubated and placed on mechanical ventilation. Before incubation, PaO2 was 58 percent (reference range not provided) and PaCO2 was 31 percent (reference range not provided) on 12-liters oxygen via a reservoir mask. Vancomycin and trimethoprim with sulfamethoxazole (Bactrim) were administered. Methylprednisolone (Solu-Medrol) 500 mg per day was given for three days and Neutrogin was increased to 250 ug. On [redacted], chest CT continued to show infiltrates in all lung fields. The patient was treated with pulse therapy of steroid (Solu-Medrol) for three days. Virus screening reported negative for urine pneumococcal antigen, adenovirus (PCR), cytomegalovirus, Pneumocystis carinii (PCR), mycoplasmal antigen, and tuberculosis bacillus. Beta-D-glucan increased to 33.7 (reference range and units were not provided). On [redacted], chest CT and chest x-ray showed that infiltrates (consolidation) were still present in all lung fields, and the patient was remained intubated to maintain the oxygen saturation at 90 percent. On [redacted], KL-6 was 6498 (reference range less than or equal to 500). On [redacted], chest CT showed moderate improvement in the infiltrates (consolidation) in all lung fields, but an interstitial pattern was still present. Cranial CT revealed hemorrhage and infarction, with lesions indicting possible Aspergillus infection. On [redacted], the patient was intubated and the fractional concentration of oxygen in inspired gas (FiO2) was 40 percent. It was decided that the patient was not to be re-intubated. Chest x-ray showed a reduction in the density of the infiltrates (consolidation) in all lung fields, but the interstitial pattern was still present. On [redacted], bacteraemia was noted with positive blood culture for multi-drug-resistant Pseudomonas aeruginosa. On [redacted], the patient expired. The cause of death was pneumonia and Aspergillus infection. The autopsy findings included increased lung weight, consolidation of the lung and disseminated Aspergillus lesions in the brain. The physician stated that the event could not be diagnosed as interstitial pneumonia and the diagnosis of pneumonia was appropriate at the time of reporting. The causal relationship between the event and VELCADE was unknown. Although the patient had Aspergillus infection as medical history, pneumonia presented drastically and expansion of shadow on lung was seen other than organizing pneumonia region. As moderate effect with steroid was seen, drug-induced pneumonia could not be totally excluded. Due to a temporal association between the onset of the events and administration of VELCADE, a causal relationship could not be excluded. VELCADE therapy was permanently discontinued. Outcome was reported as fatal. Additional information has been requested. 02-Aug-2005; On 02-Aug-2005, new information on this case was received from the investigator and included additional concomitant medications, lab data, treatments, updated dose of VELCADE, event of sepsis as cause of death and secondary immunodeficiency. The patient was Japanese. Concomitant medications included itraconazole (Itrizole), acyclovir (Astric), trimethoprim with sulfamethoxazole (Baktar), valsartan (Diovan), amlodipine besilate (Amlodin), and insulin lispro (Humalog). Additional laboratory findings included Beta-D-glucan of < 6 when measured on [redacted] and as high as 33.7 on [redacted] (units and reference range not provided). Beta-D-glucan was 12.94 on [redacted] and trended down to < 6 on [redacted] (units and reference range not provided). Aspergillus antigen of 0.5 on [redacted] and was increased to 1.5 on [redacted] and fluctuated within the same range and was noted to be 1.5 on [redacted]. The patient received 1.0 mg/m2 (1.75 mg) of VELCADE. The treatments received by the patient included ceftazidime (Modacin) and panipenem (Carbenin) for sepsis; clarithromycin, clindamycin phosphate, pazufloxacin mesilate (Pasil), micafungin sodium (Funguard), fosfluconazole (Prodif) and gamma globulin for pneumonia; lenograstim for neutropenia; methylprednisolone sodium succinate (Solu-Medrol) for interstitial pneumonia; sulfamethoxazole with trimethoprim for Pneumocystis carinii prophylaxis (PCP) and

	amphotericin B (Fungizone) for Aspergillus brain abscess. On (b) (6), the patient's respiratory condition was stable and re-intubation was not required. White Blood Cell (WBC) count was 400. Fever was more than 38.5 degrees Celsius. Her level of consciousness was 11-10 (Japan Coma Scale). On (b) (6), the patient had a fever of 39.2 degrees Celsius. WBC count was 300 and C-Reactive Protein (CRP) was elevated to 11.9. The following day, her respiratory condition deteriorated and her oxygen was increased to 12L and SpO2 was 90%. Chest x-ray revealed increased infiltrates (consolidation), and the patient received methylprednisolone pulse therapy. Subsequently on (b) (6), the patient's blood pressure dropped and she expired at (b) (6). In addition to Aspergillus infection and pneumonia, sepsis was also considered as one of the causes of death. Per investigator, the event was likely related to VELCADE because the patient presented with lesions throughout the lung fields, had an acute course and responded slightly to steroid pulse therapy. It was noted that although the sputum culture was negative for Pneumocystis carinii and Aspergillus PCR was also negative, patient's pneumonia may still have been fungal or Pneumocystis carinii pneumonia as beta-D-glucan was elevated. In addition, other etiology of pneumonia could not be ruled out as improvement on x-ray and CT scan were noted after treatment with trimethoprim combined with sulfamethoxazole or micafungin and likewise some improvement with methylprednisolone semi-pulse therapy was seen. No further information for this case is expected. 18-Oct-2005: On 18-Oct-2005, new information for this case was received from the physician and included diagnostic test results, pathological findings, an additional concomitant medication and the physician and pulmonologist's comments. Chest x-ray showed improvement on (b) (6). Per the pathologist the pathological findings in the lungs included acute and organizing diffuse alveolar damage (DAD); no Aspergillus; and dispersed bacteria, which were not the direct cause of death. Between Cycle 1 and Cycle 2 of VELCADE therapy, the patient received dexamethasone 40 mg for four days for the treatment of multiple myeloma (b) (6), mainly because she did not respond to VELCADE. This might have contributed to the improvement of diffuse alveolar damage (DAD), which was the patient's first lung-related episode ((b) (6)). With hindsight, it was undeniable that the patient might have received additional doses of VELCADE (Cycle 2) when she was already recovering from the first lung-related episode ((b) (6)), and thereby ended up being re-challenged with VELCADE. Findings from the clinical imaging of the first episode revealed that the patient experienced acute and diffuse ground-glass opacity increase, bilateral pleural effusion and respiratory tract edema. Cardiomegaly was suspected in the plain x-ray. Acute cardiogenic pulmoary edema was the most susppected findings of CT (computed tomography) imaging. The second episode revealed consolidation in the right lung, mainly, and rapidly spreading to the left lung. CT image showed unilateral co-existence of the consolidation which tended to superimpose and increased the ground-glass opacity, mainly consolidation. Lung lesion (more likely to be infectious) was found in the CT imaging. The patient showed a complete response to steroids, and the consolidation was improved. If the second episode is considered as an expression of bacterial or fungal pneumonia, inflammatory response and pyrexia was too mild, and they were different from infectious disease symptoms. Usually in the case of cardiogenic pulmonary edema and lung infection, the associated feature usually contradicts with the clinical course. The pulmonary edema-like alteration in the first episode and the pneumonia-like alteration in the second episode completely responded to dexamethasone (Decadron) and steroid pulse respectively. In the progression of the two, thickening of the respiratory tract wall and narrowing of lumen were noted. Considering these facts, it is impossible to consider the symptoms noted in the clinical course as well as the image findings as "typical" cardiogenic pulmonary edema or lung infection. Alternative causes such as drug induced lung disorder can not be denied. No further information is expected for this case. 21-Nov-2005: New information on this case was received from the physician on 21-Nov-2005 and included autopsy report results (with pathological anatomical diagnoses) and a general overview of the case. New events (respiratory failure and thromboembolism) were coded as a result of this information. The patient with multiple myeloma was post chemotherapy condition including autologous peripheral hematopoietic stem cell transplant and VELCADE. The patient's medical history included diabetes mellitus insulin-dependent. The patient died due to multiple hemorrhagic cerebral infarctions (cerebrum, cerebellum) considered to be caused by thromboembolism, and respiratory failure considered to be caused by sepsis and diffuse alveolar damage. The pathological anatomical diagnoses included multiple myeloma (IgG - gamma), diffuse alveolar damage, sepsis, multiple hemorrhagic cerebral

	infarctions (cerebrum, cerebellum) due to embolus, and diabetes mellitus insulin-dependent. Autopsy findings included ecchymoses seen diffusely in the abdominal wall skin and precordial skin. Both lungs were scleroid. Congestion and edema were remarkable. Petechiae and ecchymoses were seen diffusely. Air space was decreased in the cleavage plane and the upper lobe was white and solid but congestion was remarkable in the dorsum. Hemorrhagic nodes with petechiae and ecchymoses were diffuse. The cleavage plane was slimy and a depositional state of fibrin was assumed. The diffuse formation of a thick hyaline membrane was seen in the pulmonary alveolar pathway and pulmonary alveolar lumen histologically. Alveolar epithelium exfoliated and showed mild swelling of nucleus. Intra-alveolar hemorrhage, squamous metaplasia, and glandular metaplasia were seen partly. Air space was dilating mildly and involved immature granulation like fibrosis, which seemed like covering inlet of the pulmonary alveolar, in the pulmonary alveolar athway of both upper lobes. It was considered to be diffuse alveolar damage in the transition stage from exudate to organizing period. Massive bacteria of Gram stain positive were seen in the fibrin, which partly deposited in the air space. No fungus was confirmed. No cerebral edema was seen on the brain surface. In the parietal-occipital lobes, subarachnoid hemorrhage was found on the brain surface. There were some well-defined, fresh hemorrhagic foci scattered in the cerebral parenchyma. Some ecchymoses, approximately 7 millimeters in diameter, were found predominantly in the cerebral white matter. There was focal subarachnoid hemorrhage, which extended into the cerebral cortex, forming an ecchymosis, approximately 13 millimeter in diameter. Some ball hemorrhages were scattered also in the basal ganglia. There were fresh hemorrhagic foci, 9 millimeters and 7 millimeters in diameter, in the right cerebellar cortex and white matter. There was no remarkable change in the pontine and the substantia nigra of the midbrain and the locus ceruleus were normal. Histological findings of the brain examination suggested hemorrhagic infarction caused by embolus; however, fungal hyphae were not found. The findings were also compatible with those of sepsis. Bacterial tests of the lungs showed Enterococcus, Gram-positive rods and Pseudomonas aeruginosa from a paratripsis of the right lung lower lobe. No further information for this case is expected. 28-Dec-2005: On 28-Dec-2005, new information was received from translated survey results conducted by the Japanese Society of Hematology and the Japanese Society of Clinical Hematology (06-Dec-2005), a translated article entitled "An Unapproved Blood Cancer Drug 'VELCADE;' Multiple Deaths Occurred Among Users; Risk of Severe Lung Disorders" published in the 11-Dec-2005 issue of Asahi Shimbun newspaper, and a translated report entitled "Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma." This report refers to the second of nine patients. According to the report, the patient was diagnosed with multiple myeloma IgG-type and underwent autologous peripheral blood stem-cell transplantation (auto-PBSCT) following melphalan 200 mg/m2. She had no history of smoking. She had a history of invasive pulmonary aspergillosis, which was successfully treated with antifungal agents. Three months after auto-PBSCT, her disease recurred. She had no signs of infection, and her performance status was 1 (reference range not provided). VELCADE 1.3 mg/m2 twice a week was given for 2 weeks. Cough and dyspnea developed 8 days after completion of VELCADE. Oxygen saturation dropped to 87%, and her chest CT revealed bilateral pleural effusions. Peripheral leukocyte count was 5,600 /uL (reference range not provided). Oxygen and diuretics did not improve her condition. After dexamethasone 40 mg for 4 days, her respiratory symptoms disappeared. The second course of VELCADE was started at the same dose on Day 23 of the first course. On day 12 of the second course, she developed recurrent cough, asthma-like symptoms, fever and dyspnea. Chest CT showed bilateral infiltrates, which rapidly spread to the entire lung fields. Infection was not identified with sputum cultures. She received G-CSF, beta-lactams, carbapenems, fluconazole, itraconazole, acyclovir and amphotericin B. Although her resipratory symptoms temporarily improved with methylprednisolone 125 mg - 1000 mg for 3 days, she died of respiratory failure. Autopsy showed diffuse hyaline membranous changes with partial organization in alveolar cavity and its airway. Pathological diagnosis was consistent with acute and organizing diffuse alveolar damage. It was suggested that VELCADE "may cause lung injury." An "association between respiratory failure and VELCADE" due to the exacerbation of respiratory failure following the second course was also suggested. According to the newspaper article, the patient experienced "severe lung disorder" and died. The causal relationship with VELCADE was "suspected." As reported in the survey results, the patient experienced "serious pulmonary disorder" and died, which was determined to be "possibly related" to VELCADE. No further information is

	expected for this case. 03-Feb-2006: On 03-Feb-2006, new information on this case was received that included additional events and concomitant medications. On (b) (6), the patient was noted to have Campylobacter jejuni on venous blood test. In addition, the patient also had fever of 38.2 degrees that was resolved after treatment with dexamethasone sodium phosphate (Decadron) for multiple myeloma on the same day. Fever was considered to be a side effect of VELCADE. Relationship between sepsis and lung disorder was not established as the patient was noted to have been experiencing lung disorder when Campylobacter was detected. No further information is expected. Case Comment:
4952195	Intracranial hypertension[Intracranial pressure increased] Incorrect route of administration[Incorrect route of drug administration] Condition aggravated[Condition aggravated] Coma[Coma] Inhalation pneumopathy[Lung disorder] Case Description: Case reference number 2005-02553 is a spontaneous report referring to a female aged around 60 years (initials not provided), reported by a physician via a partner company. The patient was diagnosed with multiple myeloma on unknown date, located in spinal cord and therefore was paraplegic. Information on prior therapies, medical and allergy history, concomitant medications and concurrent disorder was not provided. The patient received VELCADE intrathecal by routing error (Dose, Cycle and Day of last administration prior to onset date of event not provided), in combination with methothrexate-melphalan-hydrocortisone intrathecal once on 12-Dec-2005. At time of this report i.e. one hour later, the patient had not experienced any adverse event. Further information on clinical course, condition of the patient and the puncture for study drug was not provided. The outcome of incorrect route administration was not reported. Information on de-challenge and re-challenge with VELCADE was not applicable. Additional information has been requested. 15-Dec-2005 On 15-Dec-2005 new information on this case was received and included information on patient's condition, new serious adverse events with onset dates: Information on patient's concurrent medical disorder included myeloma meningitis. The patient presented with myeloma meningitis before VELCADE injection. 48 hours after VELCADE injection the patient developed intracarnial hypertension. Blood pressure values were not provided. On (b) (6) the patient died due to aggravation of the disease. Information on autopsy was not reported. At time of this report it is still unclear, whether the concurrent medical disorder myeloma meningitis, the serious adverse event intracranial hypertension or the aggravated condition, led to patient's death. Additional information has been requested. 02-Mar-2006: On 02-Mar-2006 additional information was received including the patient's initials and age, two further events, details on VELCADE administration, course of events, diagnostic test results, and a cause of death. This report refers to a female patient aged 61 years (EB). It was reported that the patient had no other relevant medical history. The patient received VELCADE at a dose of 2.3 mg intrathecal. No adverse event was observed in the following hours. VELCADE was discontinued. Two days later, the patient developed intracranial hypertension with somnolence and then coma. This clinical picture was aggravated by an inhalation pneumopathy. Brain CT scan (on unknown date) revealed an important tissular mass evoking a myelomatous tumor. The patient died on (b) (6) from intracranial hypertension. The investigator considered the events of intracranial hypertension, aggravated condition, coma, and lung disorder as not related to treatment with VELCADE. No further information is expected regarding this case. Case Comment:
4991128	Medication error
4991142	Drug administration error
5049508	Incorrect drug administration rate
5074769	Drug toxicity - accidental overdose effect[Accidental overdose] Drug toxicity - accidental overdose effect[Drug toxicity] Troponin increased[Troponin increased] Intra alveolar haemorrhage[Pulmonary alveolar haemorrhage] Myocarditis[Myocarditis] Respiratory dysfunction[Respiratory disorder] Acute renal failure[Renal failure acute] Hypotension[Hypotension] Death due to septic shock[Septic shock] Thrombopenia[Thrombocytopenia] Heart failure[Cardiac failure] Pulmonary edema[Pulmonary oedema] Nausea[Nausea] Acidosis lactic[Lactic acidosis] Case Description: Case reference

	number 2006-00762 is a spontaneous report referring to a male patient of unknown age (initials not provided), reported from a physician via a partner company. The patient was diagnosed with multiple myeloma on unreported date. Details on prior therapies for underlying disease, patient's medical history, concurrent disorders, concomitant medications and allergy history were not provided. The patient received VELCADE (dose, route of administration and therapy dates not provided). On (b) (6), the patient presented with pyrexia. One day later, on (b) (6), the patient received 2 injections (2.4 mg each) of VELCADE erroneously with an interval of 15 minutes between the injections. Unknown time after the two injections, the patient was hospitalized in intensive care unit and experienced unspecified respiratory dysfunction, acute renal failure, hypotension and lactic acidosis (overdose effect). On (b) (6), the patient had a body temperature of 40 degrees Celsius. After the erroneous administration of the two doses of VELCADE, the patient experienced acute renal failure with a creatinine value of 260 mol/l (reference range not provided). His blood pressure was 60 mmHg. The patient was intubated and reanimation treatments were installed. Further details on the clinical course of the events of overdose effect, respiratory dysfunction, acute renal failure, hypotension and lactic acidosis were not provided. Action taken with VELCADE was not reported. At the time of this report, the outcomes of the events of overdose effect, respiratory dysfunction, acute renal failure, hypotension and lactic acidosis were reported as unknown. De-/re-challenge of VELCADE was reported as not applicable. Additional information has been requested. 06-Apr-2006 On 06-Apr-2006 new information on this case was received from the reporter via a partner company and included the additional SAE term of troponin increased and further details on the events. The renal function and respiratory state of the patient seemed to have improved since transfer of the patient to the intensive care unit. Nevertheless, a biological work-up showed an increase of troponin (value not provided), but echocardiography was normal. A myocarditis was suspected. Additional information has been requested. 11-Apr-2006 On 11-Apr-2006 new information on this case was received from the reporter via a partner company and included patient's initials, information on course of the event of increased troponin, and an additional SAE term. Patient's initials were (b) (6). According to the reporting physician the troponin values of the patient slowly decreased, but the patient developed severe thrombopenia (onset date not reported) that required platelet transfusion. Additional information has been requested. 19-Apr-2006 On 19-Apr-2006 new information on this case was received from the physician via a partner company and included the new SAE term of death. On (b) (6), the patient died from unknown cause. It was not reported whether an autopsy was performed. Additional information has been requested. 27-Apr-2006 On 27-Apr-2006 new information on this case was received from the physician via a partner company and included patient's age and medical history, information on treatment with VELCADE, details on clinical course of the events with additional SAE terms and cause of patient's death. At onset of the events, the patient was aged 73 years. Medical history included pyrexia. The patient received VELCADE 1.3 mg/m2 twice per week. On (b) (6) (Cycle 1, Day 11), previously reported as (b) (6), the patient received the two injections of VELCADE in error. The physician clarified that the patient has not experienced pyrexia of 40 degrees Celsius prior to hospitalization (as previously reported). The patient was dialysed due to the event of acute renal failure. On unreported date, the patient experienced intra-alveolar hemorrhage and myocarditis then septic shock due to Escherichia coil and to Candida (NOS). On (b) (6), the patient died from Septic shock to Candida. The reporting physician confirmed the life-threatening nature of the events. Additional information has been requested. 06-Jun-2006 On 06-Jun-2006, new information on this case was received from the Regional Pharmacovigilance Center of Paris Creteil via the French Agency for the Safety of Health Products (Afssaps) via a partner company and included additional events. The medically significant events of heart failure and pulmonary oedema were added. No further information for this case is expected. Additional information received 24-JUL-2006: The patient had a medical history of immunoglobulin D myeloma diagnosed in 2003. On 27-MAR-2006 the patient received the first injection of bortezomib (VELCADE) 2.4mg. On (b) (6) the second injection of VELCADE 2.4mg was administered, however later the same day a second nurse injected the patient in error with VELCADE 2.4mg. The following day the patient experienced nausea, hypotension then lesional oedema, and was hospitalised in resuscitation services. He was intubated and ventilated due to heart failure with pulmonary oedema, and ten days later the died. Case Comment:

5119455	Inadvertent exposure to drug[Accidental exposure] Cough[Cough] Chest pain[Chest pain] Case Description: Case reference number 2006-02345 is a spontaneous report referring to a female patient (ethnicity not provided) in her 50's (BH), reported by a nurse. The patient's medical history included mitral valve prolapse, for which she received antibiotic prophylaxis during dental procedures. The patient was not taking any concomitant medications. The patient's allergy history was not provided. On 08-Sep-2006, the patient, an oncology nurse, was preparing a dose of bortezomib (VELCADE), using a 3.5 mg vial, in a laminar flow hood. During preparation, the VELCADE aerosolized and the patient accidentally inhaled a small amount of the aerosol (exact amount not known). The patient was asymptomatic at the time and continued her work for the day. In the evening of 08-Sep-2006, the patient experienced a persistent dry cough (intensity not provided). On 09-Sep-2006, the patient presented to the emergency room (ER) with a complaint of a medically significant cough and ache occurring across her chest, described as "pressing chest pain" (onset date and intensity not provided). An electrocardiogram (EKG) and chest x-ray were done (results not available). The patient was treated for the cough with nebulization (medication and dosage not provided) that provided symptomatic relief; however, the cough continued. Copies of the Material Safety Data Sheet for VELCADE and VELCADE package insert were sent to the nurse via fax. An associated product complaint report was filed (see VEL-26782-PC). Action taken with VELCADE was not applicable as patient was accidentally exposed. The nurse reported the events cough and chest pain as ongoing but improved as of 09-Sep-2006. Additional information has been requested. 20-Sep-2006: On 20-Sep-2006, it was determined the medically significant event of inadvertent exposure to drug should also have been captured as serious adverse event. Additional information has been requested. 20-Sep-2006: On 20-Sep-2006, new information was received from the patient and included relevant test results and event outcomes. On the morning of 06-Sep-2006, the patient was reconstituting a vial of VELCADE under a laminar hood. When she withdrew the needle from the vial, the reconstituted VELCADE "squirted like a geyser" and she inhaled some. On 07-Sep-2006, the patient did not experience any symptoms. On 08-Sep-2006, the patient experienced a persistent cough and burning in her throat and chest "like heartburn." On 08-Sep-2006, she presented to emergency room (ER). A chest x-ray was done with normal results and an electrocardiogram (EKG) showed flipped T wave, which may be normal in some people. She was given a nebulizer to relieve her cough. The events chest pain and cough completely resolved on 08-Sep-2006. Additional information has been requested. Case Comment:
5188531	Inadvertently given VELCADE[Wrong drug administered] Difficulty writing[Dysgraphia] Difficulty walking[Gait disturbance] Dizziness[Dizziness] Vomiting[Vomiting] Numbness from nipple line down[Hypoaesthesia] Peripheral neuropathy[Neuropathy peripheral] Pain in limbs[Pain in extremity] Nausea[Nausea] Orthostatic hypotension[Orthostatic hypotension] Case Description: Case reference number 2006-01939 is a spontaneous report referring to a White male patient aged 46 years (MR), which was reported by a nurse. The patient was diagnosed with colon cancer (date not provided). Concomitant medications included oxaliplatin, folinic acid (Leucovorin), fluorouracil (5-Fluorouracil), paracetamol and oxycodone hydrochloride (Percocet). Prior therapies, additional medical history, prior hospitalizations and allergy history were not provided. The patient inadvertently received bortezomib (VELCADE) 10 mg intravenously instead of bevacizumab (Avastin) on (b) (6). Within 24 hours, the patient experienced dizziness, vomiting, difficulty walking, difficulty writing, numbness from his nipple line down, peripheral neuropathy and pain in his limbs (intensities not provided). On (b) (6) the patient was inadvertently given VELCADE 10 mg intravenously instead of Avastin10 mg intravenously in a treating hospital. On (b) (6) the patient also received oxaliplatin, leucovorin, 5-fluorouracil and Percocet as part of his regimen with Avastin. Within 24 hours, the patient began to experience dizziness, vomiting, difficulty walking, difficulty writing, numbness from nipple line down, peripheral neuropathy and pain in limbs. On (b) (6), the patient was hospitalized and was given intravenous hydration (unknown type and duration). The patient was discharged on (b) (6). On 18-Jul-2006, the patient presented to his treating clinic and an investigation revealed that the nurse who administered the VELCADE did not realize that she had administered the incorrect drug until another nurse noticed that three vials of VELCADE had been taken from the stock and found the vials in the room where the patient had been treated on (b) (6). Action taken with VELCADE was not

	applicable since the patient is no longer receiving VELCADE. The status of the events was not provided. The physician reported that the events dizziness, vomiting, difficulty walking and writing, numbness, peripheral neuropathy and pain in limbs were related to treatment with VELCADE. Additional information has been requested. 22-Aug-2006 On 22-Aug-2006, new information was received from the treating physician and included medical history, prior therapies and clinical course details. The patient's medical history included diarrhea, palmar-plantar erythrodysaesthesia syndrome, stomatitis, nausea, anorexia, abdominal pain, pain, insomnia, fatigue, dysuria, osteoarthritis, left ankle fracture, Grade 1 peripheral neuropathy, proctoscopy and endoscopic retrograde cholangiopancreatography. Prior therapies included chemotherapy, radiotherapy and resection of the rectum. The patient received chemotherapy treatment presumed to be VELCADE 10 mg on (b) (6). On (b) (6), the patient had some slight indigestion. On (b) (6) (Day 2), the patient took his son to the movies and "vomited buckets", estimated to be eight cups of green vomitus. On (b) (6) (Day 3), he was too weak to go to have his pegylated (PEG) filgrastim (Neulasta) shot and Huber needle removed. He felt dizzy, which was described as "a compression on the head" and not true vertigo". He felt the same on Days 4 and 5. On (b) (6) (Day 6), the patient mobilized himself and was taken to the hospital. It was hard for him to walk and he blacked out in the emergency room. He was diaphoretic along with rigors; consequently, he was admitted. He was treated with fluids. The PEG filgrastim was given. On (b) (6) (Day 7), the patient developed intense pain all over. He had numbness in his hands and feet and seemed to have no control of them. He also had complaints of insomnia. On (b) (6) (Day 8), he was discharged; and he was told, that if anything, he got too little of this chemotherapy. The recorded doses seemed to indicate that he received 85 mg and not 85 mg/m^2 of oxaliplatin and 10 mg of bevacizumab (Avastin). However, an oncology nurse at the hospital investigated the adverse reaction and found there were three missing vials of VELCADE. The nurse who administered the therapy reported that she had mixed the VELCADE, but she then threw it away and had used only 10 mg of Avastin. Based on the total picture, the treating physician presumed the patient received 10 mg of VELCADE and developed myalgias and peripheral neuropathy from the administration. Treatment was determined to be supportive as there was no particular antidote. The myalgias, neuropathy and nausea and any excess myelosuppression were suspected to improve over time although the improvement of the neuropathy was considered hard to predict. On 21-Jul-2006, the patient was seen on an outpatient basis for a blood draw from his port-a-cath. The patient was very weak (intensity not provided) and needed assistance from his chair. The treating physician considered that oxaliplatin could have possibly contributed to the patient's peripheral neuropathy. The status of the events dizziness, vomiting, difficulty walking and writing, numbness, peripheral neuropathy, pain in limbs, nausea and orthostatic hypotension were not provided. Additional information has been requested. 21-Sep-2006 On 21-Sep-2006, new information was received and included responses to follow up queries. The patient received 85 mg total of Oxaliplatin along with the suspected administration of VELCADE. The correct oxaliplatin dose was 85 mg/m^2 every 2 weeks. The patient was in Cycle 4 of his chemotherapy and all previous chemotherapy cycles had been uneventful. Overall, the events had not improved. The patient continued to experience hypotension and was started on fludrocortisone acetate (Florinef). His sensorimotor neuropathy had not improved and he continued to have ataxia. The reporter stated that an investigation regarding the suspected administration of VELCADE was underway. The nurse who supposedly administered the 10 mg of VELCADE had reiterated that she had thrown out the reconstituted vial prior to administration. However, the investigation revealed that the discarded "bag" was empty, which may point to the evidence that the VELCADE was actually administered. The investigation was continuing. Additional information for this case is expected. 09-Oct-2006 On 09-Oct-2006, new information was received from the treating physician and included the status of the events. On 28-Sep-2006, the physician evaluated the patient and reported no improvement in his peripheral sensory motor neuropathy or dysautonomia. The patient was scheduled to be evaluated at another hospital to assess whether it would be possible to resect the focus of adenocarcinoma in the liver with curative intent and to address his disability from his presumed VELCADE overdose. Additional information is expected. 03-Nov-2006 On 03-Nov-2006, new information was received via telephone contact with the treating physician's office and included status of the events and status of the accidental VELCADE administration investigation. The patient was seen approximately one month ago and continued to experience pain, severe motor and

	sensory neuropathy, urinary retention, and orthostatic hypotension. He is restricted to a wheelchair and was able to only walk short distances from the wheelchair to the bathroom. The patient continued to have a Foley catheter for his urinary retention. He continued to have orthostatic hypotension with his last office visit blood pressure recorded as 80/48 mg/Hg (date and reference range not provided). The patient continued on Florinef. The patient was started on irinotecan for his colon cancer (date not provided) and may be scheduled for a liver metastases resection. The investigation regarding the accidental VELCADE administration was still ongoing. Additional information for this case is expected. 05-Dec-2006 Further review of source documentation received on 22-Aug-2006 revealed the following laboratory results performed on 28-Jul-2006: cerebrospinal fluid (CSF) red blood cells (RBC) 485 (high), CSF fresh RBC 100%, CSF crenated RBC 0, CSF white blood cells 2, CSF netrophils 35% (high), CSF lymphocytes 23% (low), CSF mono/macro 42%, CSF protein 163 (high), CSF glucose 71 (units and reference ranges not provided), and CSF oligoclonal bands 1 (units and reference ranges not provided). On 05-Dec-2006, new information was received from the treating physician and included relevant test results, treatment details, status of the events and status of the accidental VELCADE administration investigation. The patient continued to be followed by an outside hospital. On 03-Aug-2006, the patient underwent magnetic resonance imaging (MRI) of the brain, which was unremarkable and MRI of the thoracic spine, which revealed low signal throughout the vertebral bodies on both T1 and T2 weighted sequences raising the question of a marrow replacement process. Correction with clinic findings was needed. There was also a mild compression deformity involving the superior T8 endplate. There was no focal disk herniation or significant canal or neural formaminal stenosis. The thoracic cord was unremarkable in appearance. On 04-Aug-2006, a nerve conduction study of the upper extremities revealed evidence of very mild damage to the right median nerve at the wrist. This was comparable to findings done one week previously. In the lower extremities, no abnormalities were noted. No other autonomic testing or nerve conduction studies were performed after the study in early August 2006. As of 02-Oct-2006, the patient continued to experience pain, numbness and neuropathy from the chin distally. He required custodial care. On 08-Nov-2006, the patient was still on Florinef, had severe peripheral neuropathy and had a Foley catheter. The patient was seeing a chronic pain consultant. On 08-Nov-2006, the patient had a blood pressure of 148/88 mm/Hg. On (b) (6), the patient underwent an elective surgical procedure for resection of the hepatic tumor, which was thought to be restricted to one lobe of the liver. However; during surgery, a few other nodules were found scattered throughout the liver and the tumor was thought to be non-resectable. No surgery was performed. The patient was on a chemotherapy regimen of leucovorin, 5-fluorouracil and irinotecan. The accidental VELCADE administration investigation was still ongoing as of 05-Dec-2006. No further information is expected for this case. Case Comment:
5228543	Overdose[Overdose] Death[Death] Congestive heart failure[Cardiac failure congestive] Case Description: Case reference number 2007-00056 is a spontaneous report referring to a male aged 62 years (ML), reported by a consumer. The patient was diagnosed with multiple myeloma on an unknown date and prior therapies were not reported. The patient's medical history included cardiac failure congestive associated with the resuscitation of the patient (the patient had died and was revived) and pneumonia. Prior hospitalizations and concomitant medications were not reported. The patient received bortezomib (VELCADE) on (b) (6) for the treatment of multiple myeloma. The patient's first dose was inadvertently administered as 6mg. The following day the patient died, and the cause of death was not known. It was reported that the patient's death was associated with an overdose, and at the time of the report it was not known whether an autopsy was performed. The reporter did not provide a causality assessment between the events and VELCADE treatment. Additional information was received on 19-JAN-2006: The patient's previous experience of congestive heart failure was reported as being a year prior to VELCADE administration, and at the time of VELCADE administration he was suffering from pneumonia. It was added that following the overdose the patient developed congestive heart failure. There was no causality assessment reported between the events and VELCADE administration Case Comment:
5343439	Accidental Exposure[Accidental exposure] Vomiting[Vomiting] Abdominal pain[Abdominal pain] Case Description: Case reference number 2007-01623 is a spontaneous report referring to a female aged 2 years, reported by a physician via a toxicological centre. The patient's medical history,

	prior therapies and concomitant medications were not reported. The patient accidentally took bortezomib (VELCADE) orally on 18-MAY-2007 and the amount of VELCADE taken was not reported. Subsequently, on an unknown date, the subject experienced vomiting and abdominal pain. VELCADE exposure was withdrawn and the corrective treatments given were not reported. At the time of report, the outcome of the events was unknown. The reporter assessed the events as possibly related to VELCADE. Case Comment:
5397127	The patient received an overdose of the VELCADE in that he was given the entire vial with each administration[Overdose] Edema[Oedema] Severe neuropathy[Neuropathy] Case Description: Case reference number 2007-00784 is an investigator initiated clinical trial report from study i34103-043, Total Therapy III: A Phase II Study Incorporating Bone Marrow Microenvironment (ME) - Co-targeting Bortezomib into Tandem Melphalan-Based Autotransplants with DT PACE for Induction/Consolidation and Thalidomide + Dexamethasone for Maintenance. The report refers to a male patient (age and ethnicity not provided). The patient was being treated with bortezomib (VELCADE), in which the calculated dose was 1.0 mg/m2 (route not provided). The patient was inadvertently overdosed with 1 vial per dose on days 1, 4, 8 and 11 for the past 7 months, and experienced severe neuropathy and edema (intensities and dates of onset not provided). Action taken with VELCADE was not provided. The causality for the events drug overdose accidental, severe neuropathy and edema was not provided. Additional information has been requested for this case. 30-Mar-2007: On 30-Mar-2007, new information was received for this case from the investigator which included patient identifiers, indication for treatment with VELCADE, VELCADE dates and dosage information, medical history, concomitant medications, onset and resolution date for the event Medication Administration: Incorrect dose of bortezomib given at local Sub-Investigator's office (incorrect dose administered), causality for the event incorrect dose administered and additional information with regards to the event. The patient (b) (6) was a 57 year old white male, who was diagnosed with multiple myeloma, lalmbda light chain d, stage IIIA, in April 2005. On 30-Jun-2005, the patient enrolled in UARK 2003-33 Total Therapy III regimen, which included bortezomib (VELCADE), dexamethasone, thalidomide, cisplatin, doxorubicin (Adriamycin), cyclophosphamide and etoposide (VDT Pace). He completed both VDT Pace induction cycles on 01-Jul-2005 and 27-Jul-2005. His melphalan 200 transplant cycles were 08-Sep-2005 and 16-Nov-2006. The patient's consolidation cycles were 16-Feb-2006 and 22-May-2006. The patient was in maintenance Year 1, Month 1 when this event was identified. On 19-Mar-2007, a call was placed from the office to obtain orders for the patient. Furthermore, the caller stated that they had been treating the patient with a full vial of VELCADE per dose. They reported that because the label on the vial read "single dose vial", they thought he should received the entire vial. The nurse stated that the patient had been receiving 3.5 mg per dose. It was explained that the total dose should not be more than 2 mg/m2. Upon requesting the patient's height and weight, it was also reported that the patient had not been weighed in months. The patient was instructed to hold VELCADE and thalidomide dosing. An order was written for a Neurology consult and Nerve Conduction Studies for the patient. The patient was instructed to continue treatment with dexamethasone, ranitidine hydrochloride (Zantac), aciclovir (Acyclovir) and levofloxacin (Levaquin) and to return to the office as soon as possible. On 23-Mar-2007, the patient was removed from the protocol due to bortezomib violation. Last dose of VELCADE was given on 22-Feb-2007. On 19-Mar-2007, the investigator reported the event Medication Administration: Incorrect dose of bortezomib given at local Sub-Investigator's office (incorrect dose administered) as resolved. The investigator reported the event incorrect dose administered to be related to VELCADE. Additional information has been requested for this case. 25-Apr-2007: On 25-Apr-2007, additional information was received from the investigator which included status of the event neuropathy, lot numbers for VELCADE, VELCADE administration end date and intensity of the event neuropathy. The intensity of the event neuropathy fluctuated from mild to moderate (Grade 1 and 2). The status of the event neuropathy was not completely resolved as of 25-Apr-2007. Additional information has been requested for this case. 17-May-2007 and 18-May-2007: On 17-May-2007 and 18-May-2007, additional information was received for this case, which included the sub investigator's contact information, update of an event term, onset date for the events, updated status of the events, patient's height and weight, and information regarding the overdose of VELCADE administration. The patient returned for a follow up (date not provided) after receiving

	approximately 4 cycles of VELCADE, thalidomide and dexamethasone (VDT) on the 2003-33 protocol. It was then discovered that the patient was given the entire vial of VELCADE with each administration (dates not provided), which was 3.5 mg (route not provided), when the patient should have received 1.0 mg/m2. Based on this information, the event term of "medication administration: incorrect dose of bortezomib given at local sub-investigator's office" has been updated to "the patient received an overdose of the VELCADE in that he was given the entire vial with each administration". As noted per the source documents, the patient's height was 71 inches (180.3 cm) and the patient's weight was 218.5 lbs 999.1 kg). On 13-Oct-2006, the patient experienced significant peripheral neuropathy with pain all over and swelling (intensities not provided). In March 2007 (exact date not provided), the patient had an angiogram and had two stents placed as part of the workup for the "VELCADE-associated condition". The investigator reported that the patient was "much improved with probable Grade 1 to 2 peripheral neuropathy". He also reported that the lower extremity edema was largely resolved. Additional information has been requested for this case. 12-Jul-2007: On 12-Jul-2007, additional information was received for this case which included lab results and status of the events sensory neuropathy and edema. The investigator reported that the sensory neuropathy and edema fluctuated from Grade 1 to Grade 2. On 10-Jan-2007, the sensory neuropathy was a Grade 3, but improved to Grade 1 on 02-Mar-2007. Furthermore, the event edema was Grade 3 on 02-Mar-2007; however, improvement was noted upon his return visit in May. On 09-May-2007, a EMG report showed distal, sensory motor, axonal polyneuropathy. The process was chronic, but the repair was not complete. The investigator reported that the sensory neuropathy and edema were resolved. Furthermore, it was reported that the patient experienced mild discomfort; however it did not affect his ability to carry on with his daily living. No further information is expected for this case. Case comment
5455167	Administration error[Drug administration error] Case Description: Case reference number 2007-02932 is a spontaneous report from a pharmacist and refers to a patient (age and gender unknown) administering bortezomib (VELCADE), who was diagnosed with multiple myeloma on an unknown date. Prior therapies for disease under study, concomitant medication, medical history and prior hospitalizations were not reported. The patient administered VELCADE 1.5mg intravenously on AUG-2007. The patient experienced a drug administration error on 04-SEP-2007. The patient was hospitalized; the date of hospitalization has not been reported. On 04-SEP-2007 the first dos of 2nd cycle was administrated to the patient by intravenous drip. Action taken with the study medication and the outcome of the event were not reported. The reporter did not provide a causality assessment. Additional information was received on 04-SEP-2007 and on 10-SEP-2007: It was reported that the world wide receipt date was 04-SEP-2007, not 30-JUL-2007 as stated in the initial report. VELCADE was administered by intravenous drip not as an intravenous bolus. No changes were made to the previous causality assessment. Case Comment:
5911538	Patient who received almost 2 times the normal dose of VELCADE[Accidental overdose] Hypotension[Hypotension] Worsening of respiration[Dyspnoea] Case Description: Case reference number 2008-02857 is a spontaneous report referring to a male patient (age and ethnicity not provided) (b) (6) reported by a physician. The patient was diagnosed with stage II multiple myeloma on 22-Jul-2008. Concomitant medications included dexamethasone, vancomycin, midazolam hydrochloride (Versed), metoprolol, heparin, fentanyl, esomeprazole (Nexium), acetylsalicylic acid (Aspirin), allopurinol and atorvastatin. The patient's medical history included acute myocardial infarction and acute renal failure. Prior therapies, hospitalizations, and allergy history were not provided. On 30-Jul-2008, the patient received treatment with bortezomib (VELCADE) (dose not provided) via intravenous (IV) bolus. On 30-Jul-2008, the patient experienced the medically significant events hypotension and the patient received almost 2 times the normal dose of VELCADE (intensities not provided). On 30-Jul-2008, the patient received a single dose of dexamethasone 40 mg (route of administration not provided) and a higher than normal dose of VELCADE (details not provided). The dose was intended to be the first dose of the first cycle of VELCADE therapy. The patient was erroneously dosed based on a patient weight of 111 kg and a body surface area (BSA) of 2.39 m2. The patient's actual body weight was 61 kg. The patient received almost double the intended dose of VELCADE. The patient was monitored

	in the coronary care unit (CCU), where he experienced one episode of hypotension (blood pressure not provided) eight hours post VELCADE therapy. The physician could not confirm whether the hypotension was due to VELCADE. or the patient's concurrent illnesses/medical condition. Treatment with VELCADE was held due to the events. The event hypotension was ongoing and unchanged on 02-Aug-2008. Additional information has been requested. 22-Sep-2008: On 22-Sep-2008, new information was received from the treating physician and included patient information, VELCADE administration details, hypotension information, and action taken with VELCADE. The patipnt was a white male aged 71 years. He had no known drug allergy history. The patient received VELCADE 1.3 mg/m2 IV bolus on 30-Jul-2008. On 30-Jul-2008, approximately 1-2 hours after receiving VELCADE, the patient experienced an episode of Grade 2 hypotension which responded to fluid boluses. The patient's worsening respiratory status required bi-level positive airway pressure (BiPAP) initiation. The patient's hypotension resolved after 4 hours. His respiratory status improved after 12 hours. The patient underwent plasmapheresis for treatment of his symptoms on 31-Jul-2008. On 30-Jul-2008, treatment with VELCADE was reduced to the same dose based on the patient's true weight. The event hypotension was completely resolved on 31-Jul-2008. The investigator reported the event hypotension as possibly related to VELCADE. No additional information is expected for this case.
5928314	Inadvertent exposure to drug[Accidental exposure] skin lesion[Skin lesion] Case Description: Case reference number 2008-03822 is a spontaneous report referring to a female patient of unspecified age, reported by an other health professional. The patient's medical history and concomitant medication were not reported. On 09-OCT-2008, a nurse while she was preparing VELCADE injection for a patient, a part of drug was dropped on her arm. She washed her arm with water but a skin lesion was developed, which was assessed as medically significant . At the time of the report, corrective treatment, and outcome of the event were not reported. The reporter did not provide the causality assessment between the event and VELCADE therapy.
5955997	Inadvertent overdose[Accidental overdose] Tumor lysis syndrome[Tumour lysis syndrome] Peripheral neuropathy[Neuropathy peripheral] Case Description: Case reference number 2008-04142 is a spontaneous report referring to a patient of unspecified gender and age, reported by a company physician following a lecture given by another physician. The patient's medical history was not reported. Concomitant medications included dexamethasone. The patient received bortezomib (VELCADE) 8 mg and co-suspect drug doxorubicin hydrochloride (Doxil) for the treatment of multiple myeloma. Therapy details were not reported. VELCADE 8 mg dose represented an inadvertent overdose. On an unspecified date, the patient was hospitalised in the intensive care unit (ICU) due to tumor lysis syndrome. Furthermore, the patient developed peripheral neuropathy on an unspecified date. The action taken with VELCADE and Doxil was not reported. On an unspecified date, the patient had recovered from the event of tumor lysis syndrome and at the time of the report, the outcome of peripheral neuropathy was not reported. The patient also experienced full remission following VELCADE, Dexamethasone and Doxil treatment. The reporter did not provide a causality assessment between the events and VELCADE therapy.
5988512	Disease progression[Disease progression] Interstitial pneumonia[Interstitial lung disease] Off label use[Off label use] Intravenous formulation administered by other route[Incorrect route of drug administration] Case Description: Case reference number 2008-04502 is a spontaneous literature report entitled "A case complicated by interstitial pneumonia following intra-arterial infusion chemotherapy including VELCADE (bortezomib) in another hospital during treatment of recurrent oesophageal carcinoma" referring to a male aged 52 years, reported by a physician. The patient was diagnosed with oesophageal carcinoma recurrent or an unknown date. The patient's medical history included subtotal esophagectomy under right thoracolaparotomy for lower thoracic oesophageal carcinoma and radiation therapy. It was unclear if patient actually received radiation therapy, and the treatment field was not reported. Concomitant medications included erlotinib hydrochloride (Tarceva), oxaliplatin, gemcitabine hydrochloride, mitomycin, pamidronate disodium (Aredia). The patient received bortezomib (VELCADE) 0.175mg intra-arterially for oesophageal carcinoma

	recurrent (off label use); therapy dates not reported. A combination of 5 unspecified drugs were also given intra-arterially (intravenous formulation administered by other route). On an unknown date, seventeen days after the arterial infusion therapy, the patient developed severe respiratory discomfort and two days later the patient was hospitalised. No increase in pleural effusion was observed and fine crackle was heard from the bilateral lung fields. A computed tomography (CT) scan showed ground glass opacities in the bilateral lung fields and the patient was diagnosed with drug-induced interstitial pneumonia. Corrective treatment included pulsed steroid therapy with methylprednisolone 1000 mg for 3 days followed by prednisolone 50mg and the symptom improved. Treatment of the interstitial pneumonia with pulsed steroids was considered successful. On an unknown date in (b) (6), the patient died from an aggravation of the underlying disease. The outcome of the event of interstitial pneumonia was ongoing with decreased intensity. At the time of report it was unknown if an autopsy was performed and the cause of death was reported as disease progression. Treatment with VELCADE was discontinued. The reporter assessed the event of disease progression as not related to VELCADE therapy. The reporter did not provide a causality assessment between the event of interstitial pneumonia and VELCADE.
6025144	Death from cardiocirculatory arrest[Cardiac arrest] Confusional state[Confusional state] Convulsive crisis[Convulsion] Drug maladministration[Drug administration error] Drug administered by inappropriate route[Incorrect route of drug administration] Case Description: Case reference number 2008-03513 is a spontaneous report referring to a male patient aged 71 years, reported by a physician via a company representative. The patient's medical history included testicular lymphoma with meningeal localisation. Concomitant medications included rituximab, cyclophosphamide, idarubicin, vincristine sulfate (Oncovin), prednisone (R-CIOP) and intrathecal methotrexate. On 19-SEP-2008, the patient accidentally received intrathecal bortezomib (VELCADE) instead of Methotrexate (Drug maladministration). On the same date the patient experienced confusional state and convulsive crisis. The events were assessed as life threatening and the patient's hospitalisation was prolonged. At the time of the report, the events of confusional state and convulsive crisis were still persisting and the patient was being maintained in a pharmacological coma. Action taken with VELCADE was not reported. The reporter assessed the events as possibly related to VELCADE. Additional information was received from a physician via the Ministry of Health in Italy, Regulatory Number: 90585. The patient's date of birth was provided. Prior therapy included rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) and periodic methotrexate with methylprednisolone (Urbason) intrathecally. VELCADE dosage received on 19-SEP-2008 was 2 mg. The physician gave the patient intrathecal VELCADE instead of methotrexate by mistake and the patient experienced epileptic seizures and profound drowsiness. Computed tomography was negative and an electroencephalogram (EEG) showed slow cerebral activity. The patient was treated with corticosteroids and transferred to the resuscitation area where he also received a sedative. At time of report, the patient had not recovered from epileptic seizure. There was no change to the previous causality assessment. Additional information was received on 30-OCT-2008: It was reported that the patient had not recovered from pharmacological coma. On (b) (6) the patient died. It was unknown whether he died of cardiac failure or from severe brain damage. The autopsy status was not reported. The reporter did not provide a causality assessment between the patient's death and VELCADE therapy. There was no change to the previously reported causality assessment. Additional information was received on 17-NOV-2008: Concomitant medication also included methyprednisolone intrathecally for an unknown indication. Causality assessment using the Naranjo algorithm was possible. There was no change to the previously reported causality assessment. Additional information was received on 01-DEC-2008: On (b) (6) (not (b) (6) as previously reported), the patient died from cardiocirculatory arrest while in resuscitation unit. There was no change to the previously reported causality assessment. Additional information received on 10-DEC-2008: The patient was diagnosed with testicular non-Hodgkin lymphoma in APR-2008. The patient was treated with intrathecal and systemic chemotherapy for diplopia caused by the probable cerebral location of the lymphoma. The patient was given VELCADE intrathecally on 18-SEP-2008 (previously reported as 19-SEP-2008). The patient was hospitalised and monitored, but was initially asymptomatic. On 19-SEP-2008, the patient experienced hallucinations and agitation and was treated with sedative drugs. The patient then

	experienced a convulsive crisis. The patient was transferred to a resuscitation area where he was intubated, had a central venous catheter inserted, started to receive empiric antibiotic therapy and was maintained in a pharmacological coma. Enteral nutrition was started on (b) (6) and a tracheostomy was performed on (b) (6). No change to the previous causality assessments was provided.
6125906	Pneumonia[Pneumonia] Septic shock[Septic shock] Renal failure[Renal failure] incorrect route of drug administration[Incorrect route of drug administration] Case Description: Case reference number 2009-00665, received on 19-FEB-2009, is a spontaneous report referring to a male patient aged 72 years, reported by a healthcare professional via a company representative. The patient was diagnosed with multiple myeloma on an unspecified date. Prior therapies for the disease included 5 cycles of melphalan, prednisolone and thalidomide (MPT therapy) and 2 doses of cyclophosphamide with no response. The patient's medical history and concomitant medications were not reported. The patient received bortezomib (VELCADE) 1.3mg/m2 (route of administration not reported) and a non company co-suspect drug dexamethasone for the treatment of multiple myeloma; therapy dates were not provided. On an unspecified date, after completion of cycle 1 and on day 11 the patient was reported to be well. However, on day 13 the patient attended accident and emergency (A&E) with vague respiratory symptoms. Subsequently, the patient deteriorated and developed septic shock, respiratory failure and renal failure. On (b) (6), 15 days after starting VELCADE treatment, the patient died and no definite cause of death was established. It was not reported whether an autopsy was performed. The reporter did not provide a causality assessment between the events and VELCADE therapy. Additional information was received on 16-MAR-2009 from a physician: The patient's demographic details were updated. The patient was 73 years of age (not 72 years as previously reported) at the time of onset. The patient was diagnosed with multiple myeloma on 01-JUL-2008 and had a medical history, which included prostate cancer and tuberculosis. Concomitant medications included dexamethasone (previously reported as a non company co-suspect drug), diltiazem, clopidogrel, atenolol, atorvastatin, valaciclovir, omeprazole and nystatin (Mycostatin). The patient received VELCADE 1.3 mg/m2 (2.6mg) subcutaneously from (b) (6) . On (b) (6), day 13 of cycle 1, the patient developed pneumonia and was hospitalised on the same day. The patient rapidly deteriorated requiring intubation and ventilation, inotropic support and dialysis. Two days after the onset of pneumonia, on (b) (6) the patient died due to the event. An autopsy was not performed. Action taken with VELCADE was not applicable. The reporter commented that the event might have occurred due to immune suppression from VELCADE and Dexamethasone therapy. There was no change made to the previously reported causality assessment.
6249165	This initial clinical report, received on 24-Apr-2009, is from a non-Bayer Investigator sponsored study, Protocol SR-06 1007/MM 14, a Phase I/II trial of Sorafenib and weekly Bortezomib in the treatment of patients with relapsed or refractory multiple myeloma. Bayer Impact/study number: 13040. Site number: 00301. Patient number: 0018486.75 year-old male patient (pt) with multiple myeloma received Sorafenib (sorafenib) 400 MG (200 MG BID) and Bortezomib (bortezomib) 1.6 mg/m2 (days 1,8,15 and 22) beginning 31-Mar-2009. Both study medications have a reported stop date of 21-Apr-2009. Oncology history: Initially diagnosed with multiple myeloma on 25-Feb-2009. History/co-morbidities: a-fib (atrial fibrillation), liver failure with previous Lenolidomide therapy, and hypertension. BSA (Body Surface Area):2.04. ECOG Performance Status: 0. Concomitant drugs: It is unknown whether any concomitant drugs have been given.On (b) (6), pt's wife called office stating pt was complaining of difficulty breathing and feeling like a weight on his chest. Wife was instructed to call 911. Pt was transported to hospital and admitted with initial diagnosis of PNEUMONIA (CTC GRADE 3). Portable chest x-ray revealed LUL (left upper lobe) pneumonia. Pt was intubated and then extubated per wife's request. Pt then expired (reported as DEATH (CTC GRADE 5)). No further information is available at this time. Autopsy information (if any) is unknown. Further information will be sent as it becomes available.Investigator considered DEATH (CTC GRADE 5) as possibly related to study drugs. Follow-up (FU) 30-Apr-2009: Additional information provided by investigator.SAE of DEATH (CTC GRADE 5) changed to CARDIOPULMONARY ARREST (CTCAE GRADE 5). Date of death amended to (b) (6).EKG on (b) (6) revealed the pt to have

	cardiomyopathy and a-fib (atrial fibrillation). He had been taking only half of his prescribed dose of sotalol. He arrested and a code was called. He was intubatedand then extubated per wife's request. Expired on (b) (6) due to CARDIOPULMONARY ARREST (CTCAE GRADE 5). Investigator considered CARDIOPULMONARY ARREST (CTCAE GRADE 5) as possibly related to study drugs and unexpected. No further information is anticipated at this time.FU 24-Jun-2009: Response to queries provided by study site.It was verified that PNEUMONIA (CTC GRADE 3) was considered an SAE by the investigator; however, causal assessment & alternative explanation were not provided. Concomitant medication page was not available. Alternative explanation for CARDIOPULMONARY ARREST (CTCAE GRADE 5) provided as pt had history of A-fib and was followed by a cardiologist.==Bayer CommentInitial report 24-Apr-2009: The fatal outcome of DEATH (CTC GRADE 5) is serious and not listed in the International Product Information of sorafenib (Nexavar; BAY43-9006) whereas PNEUMONIA (CTC GRADE 3) is serious due to hospitalization and listed (under the context of "infection") for sorafenib. The company cannot agree with the investigator who considers DEATH (CTC GRADE 5) as possibly related to sorafenib citing the lack of details regarding the primary cause of death and the fact that the patient required intubation suggests respiratory insufficiency which had not been addressed. The event PNEUMONIA was derived from unstructured information and therefore, an investigator causality assessment/alternative explanation is not available. The company has insufficient basis at this time to consider a causal association between pneumonia and sorafenib therapy citing lack of details regarding the status of the underlying malignancy, concomitant conditions and medications. Co-suspect Bortezomib, concurrent condition of increased BNP suggestive of heart failure, concurrent hyponatremia, as well as the underlying multiple myeloma, history of liver failure from past drug therapy, and cardiac arrhythmia of atrial fibrillation provides plausible alternative explanations for both events.Additional information is requested.

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/s/

ZACHARY A OLESZCZUK on behalf of TERRI WOOD-CUMMINGS
01/13/2012

ZACHARY A OLESZCZUK
01/13/2012

CAROL A HOLQUIST
01/13/2012

Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

To: Amy Baird, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion
Division of Professional Promotion

CC: Karen Rulli, Group II Leader, OPDP
Adora Ndu, Regulatory Review Officer, OPDP

Date: December 22, 2011

Re: Comments on draft labeling (Package Insert) for Velcade (bortezomib)
NDA 021602, S-027

In response to your consult dated September 29, 2011, we have reviewed the draft Package Insert (PI) for Velcade that includes changes for S-027, and offer the following comments. OPDP has made these comments using the version dated December 15, 2011.

Section	Statement from draft	Comment
Dosage and Administration, 2.5 Management of Peripheral Neuropathy Warnings and Precautions, 5.1 Peripheral Neuropathy	Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.	This claim can be used promotionally to imply that patients with pre-existing or at high risk of peripheral neuropathy using the intravenous (IV) route of administration can switch to the subcutaneous (SQ) route of administration of Velcade to reduce the incidence/occurrence of peripheral neuropathy. We note comment [A4] in the proposed PI which states that the sponsor has not provided data to substantiate these types of claims. Please revise this statement to communicate that switch data is not available.

Section	Statement from draft	Comment
Dosage and Administration, 2.5 Management of Peripheral Neuropathy Warnings and Precautions, 5.1 Peripheral Neuropathy	(b) (4)	
Dosage and Administration, 2.7 Administration Precautions	If local injection site reactions occur following VELCADE administration subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, the IV route of administration should be considered.	Are these statements supported by substantial evidence? If not, please delete. These claims can be used promotionally to imply that patients experiencing local injection site reactions from the SQ route of administration can use a less concentrated solution or switch to the IV route of administration of Velcade.
Warnings and Precautions, 5.1 Peripheral Neuropathy	In the Phase 3 relapsed multiple myeloma trial comparing VELCADE subcutaneous vs. IV the incidence of Grade ≥ 2 peripheral neuropathy events was 24% for subcutaneous and 41% for IV. Grade ≥ 3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 16% in the IV treatment group.	Please consider deleting these statements describing the rates of various Grades of peripheral neuropathy from the Warnings and Precautions section of the PI. This is repetitive since the rates for peripheral neuropathy are already included in Table 9 from the Adverse Reactions section of the proposed PI.
Adverse Reactions, 6.1 (b) (4) (b) (4)	In general, safety data were **similar** for the subcutaneous and IV treatment groups.	Is this statement supported by substantial evidence (emphasis added)?
Adverse Reactions, 6.1 (b) (4) (b) (4)	(b) (4)	We note that safety comparisons were not pre-specified; however, are the incidence rates for neuralgia, peripheral neuropathy, and thrombocytopenia clinically significant and also statistically significant? If not, please consider deleting this statement since this information is already presented in Table 9 of the proposed PI. (b) (4)

Section	Statement from draft	Comment
		(b) (4)
Adverse Reactions, 6.1 (b) (4) (b) (4)	(b) (4)	
Adverse Reactions, 6.1 (b) (4) (b) (4)		
Adverse Reactions, 6.1 (b) (4) (b) (4)	The incidence of serious adverse events was **similar** for the SQ treatment group (36%) and the IV treatment group (35%).	Is this statement supported by substantial evidence (emphasis added)?

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/s/

NISHA PATEL
12/22/2011

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	21602
Brand Name	Velcade
Generic Name	Bortezomib
Sponsor	Millennium Pharmaceuticals
Indication	Treatment of Patients with Multiple Myeloma and Mantle Cell Lymphoma
Dosage Form	Single Dose Vial Containing 3.5 mg of Bortezomib as a Sterile Lyophilized Powder
Drug Class	Antineoplastic
Therapeutic Dosing Regimen	1.3 mg/m^2 Administered S.C. or I.V. Twice Weekly (Days 1, 4, 8, and 11 of 21-Day Treatment Cycle)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1.3 mg/m^2 Administered I.V. Twice Weekly
Submission Number and Date	SDN 278 / 23 Mar 2011
Review Division	DHP / HFD 160

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in mean QTc interval (i.e., >20 ms) was detected in the trial following intravenous or subcutaneous administration of bortezomib 1.3 mg/m^2 on Day 1. The largest upper bounds of the 2-sided 90% confidence interval (CI) for the mean change from baseline in QTcF for bortezomib 1.3 mg/m^2 administered s.c. or i.v. was 4.3 and 13.3 ms, respectively. No significant concentration-ΔQTcF relationship was observed. Small increase in mean QTc interval (i.e., <10 ms) cannot be ruled out because of study design limitations.

In this open label, randomized, phase I study of 24 subjects with measurable and symptomatic multiple myeloma after at least 1 prior therapy or who had already undergone or were unsuitable for bone marrow transplantation. Subjects were randomized without stratification to receive bortezomib either as an i.v. bolus (n = 12) or an s.c. injection (n = 12). Overall summary of findings is presented in Table 1

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Bortezomib (1.3 mg/m^2 s.c. or i.v. on day 1) (FDA Analysis)

Treatment	Time (hour)	ΔQTcF (ms)	90% CI (ms)
Bortezomib 1.3 mg/m^2 s.c., Day 1	2	-3.1	-10.4; 4.2
Bortezomib 1.3 mg/m^2 i.v., Day 1	0.5	4.2	-5.0; 13.3

The purpose of this study was to characterize the cardiac safety of the two routes of bortezomib administration. The high exposure scenario is expected to occur after repeated dosing for patients co-administered strong CYP3A inhibitors (i.v. bortezomib: 40% increase in AUC, but no effect on C_{max}) or patients with moderate or severe hepatic impairment (i.v. bortezomib: 60% increase in AUC, but no effect on C_{max}).

Bortezomib s.c. C_{max} on day 1 was about25% bortezomib i.v. C_{max} on day 1. As accumulation at day 11 for i.v. and s.c. is 30% higher, the high exposure scenario for bortezomib s.c. is encompassed by day 1 exposures of bortezomib 1.3 mg/m^2 i.v.

Following i.v. administration of bortezomib 1.3 mg/m^2, C_{max} at Day 11 was 30% higher than that observed on Day 1. Large increase in mean QT interval (i.e., >20 ms) with 30% increase in exposure with repeated dosing is not anticipated as no significant concentration-QT relationship was identified for bortezomib.

2 PROPOSED LABEL

2.1 QT-IRT PROPOSED LABEL

QT-IRT recommends that following language in the label. Our recommendations are suggestions only. We defer final labeling decisions to the review division.

Section 12.2:

The effect of a single dose of bortezomib 1.3 mg/m^2 following intravenous or subcutaneous administration was evaluated in an open-label, phase I study in 24 subjects with measurable and symptomatic multiple myeloma. No large changes in mean QTc interval (i.e., >20 ms) from baseline were detected. Because of the design limitations, small increase in mean QT interval (i.e., <10 ms) cannot be ruled out.

3 BACKGROUND

3.1 PRODUCT INFORMATION

VELCADE® (bortezomib) for Injection is an ubiquitin-proteasome inhibitor, indicated for the treatment of multiple myeloma. Bortezomib was approved in 2003. The active moiety is a modified dipeptidyl boronic acid provided as a mannitol boronic ester. VELCADE is a reversible inhibitor of the chymotrypsin-like activity of the 26SA

proteasome in mammalian cells. It is cytotoxic to a variety of cancer cell types in vitro and causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma1. Specifically, VELCADE is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin 6 (IL 6) mediated cell growth, a direct apoptotic effect, and possibly antiangiogenic and other effects.

3.2 MARKET APPROVAL STATUS

Bortezomib is approved for marketing in the USA.

3.3 PRECLINICAL INFORMATION

Not submitted.

3.4 PREVIOUS CLINICAL EXPERIENCE

From Bortezomib's package insert

(b) (4)

QT-IRT datamining analysis for Torsade de pointes and QT prolongation

We conducted an MGPS data mining analysis of AEs with bortezomib associated with QT prolongation and Torsade de pointes using the AERS database. Both AEs had EBGM lower than 2 suggesting signals within background rate.

Generic name	PT	HLT	HLGT	SOC	N	EBGM	EB05	EB95
Bortezomib	Electrocardiogram QT prolonged	ECG investigations	Cardiac and vascular investigations (excl enzyme tests)	Inv	25	1.38	0.987	1.89
Bortezomib	Torsade de pointes	Ventricular arrhythmias and cardiac arrest	Cardiac arrhythmias	Card	4	0.583	0.254	1.18

Created by:	Empirica Signal Administrator
Created on:	10/05/2011 20:03:38 EDT
User:	Monica Fiszman
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 09/23/2011 00:00:00 loaded on 2011-10-05 04:18:53.0
Dimension: 2 Selection Criteria: Generic name(Bortezomib) + PT(Electrocardiogram QT prolonged, Torsade de pointes)	

Reviewer's comments: Based on package insert information no sudden cardiac deaths, ventricular arrhythmias, or clinically relevant ECGs changes were seen in bortezomib's clinical program. No postmarketing signal linked to QT prolongation was detected in our data mining analysis.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of bortezomib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT has not reviewed the protocol prior to conducting this study. The sponsor submitted the study report entitled "Comparison of Pharmcokinetics and Pharmacodynamics of Subcutaneous Versus Intravenous Administration of Bortezomib in Patient With Multiple Myeloma" for bortezomib, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Comparison of Pharmacokinetics and Pharmacodynamics of Subcutaneous Versus Intravenous Administration of Bortezomib in Patients With Multiple Myeloma

4.2.2 Protocol Number

Protocol 26866138-CAN-1004

4.2.3 Study Dates

Study initiated: January 26, 2006

Study completed: February 25, 2007

4.2.4 Objectives

- The primary objective was to characterize the pharmacokinetics (PK) of the two routes of administration.
- The secondary objectives were to characterize the pharmacodynamics (PD) (whole blood 20S proteasome inhibition), safety (including cardiac safety), and efficacy of the two routes of administration.

4.2.5 Study Description

4.2.5.1 Design

This was an open label, randomized, phase I study of subjects with measurable and symptomatic multiple myeloma after at least 1 prior therapy or who had already undergone or were unsuitable for bone marrow transplantation. Subjects were randomized 1:1, without stratification, to receive bortezomib either as an i.v. bolus (Group 1, n = 12 subjects) or an s.c. injection (Group 2, n = 12 subjects). Bortezomib was administered at a dose of 1.3 mg/m^2 of body-surface area twice weekly for 2 weeks (on Days 1, 4, 8, and 11), followed by a 10-day rest period (Days 12 to 21) without treatment, for up to 8 cycles.

4.2.5.2 Controls

No placebo or positive control was used in this study.

4.2.5.3 Blinding

This was an open label study and none of the treatment arms were blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Bortezomib was administered as an i.v. bolus or s.c. injection at 1.3 mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle.

- Group 1: Bortezomib 1.3 mg/m^2 i.v.
- Group 2: Bortezomib 1.3 mg/m^2 s.c.

4.2.6.2 Sponsor's Justification for Doses

The study was performed in the approved patient population of relapsed multiple myeloma with the approved bortezomib dose and schedule (1.3 mg/m^2 days 1, 4, 8, and 11 every 3 weeks for 8 cycles).

Reviewer's Comment: The bortezomib 1.3 mg/m^2 s.c and i.v. doses were appropriate for this study.

The high exposure scenario is expected to occur after repeated dosing for patients co-administered strong CYP3A inhibitors (i.v. bortezomib: 40% increase in AUC, but no effect on C_{max}) or patients with moderate or severe hepatic impairment (i.v. bortezomib: 1.6-fold increase in AUC, but no effect on C_{max}).

Bortezomib s.c. C_{max} on day 1 was about 25% of the bortezomib i.v. C_{max} on day 1. As accumulation at day 11 for i.v. and s.c. is 30% higher, the high exposure scenario for bortezomib s.c. is encompassed by day 1 exposures of bortezomib 1.3 mg/m^2 i.v.

Following i.v. administration of bortezomib 1.3 mg/m^2, C_{max} at Day 11 was 30% higher than that observed on Day 1. Large increase in mean QT interval (i.e., >20 ms) with 30% increase in exposure with repeated dosing is not anticipated as no significant concentration-QT relationship was identified for bortezomib.

4.2.6.3 Instructions with Regard to Meals

Doses were administered without regard to meals.

Reviewer's Comment: Dosing without regard to meals is acceptable as bortezomib is administered i.v. or s.c.

4.2.6.4 ECG and PK Assessments

The design of the study planned for the collection of PK and ECG information at multiple time points before and after bortezomib administration on Cycle 1 Day 1. ECG was only repeated on Cycle 1 Day 11 if there were technical concerns or clinical relevant findings on Cycle 1 Day 1 ECG recording. Whenever appropriate, an attempt was made to sample PK, PD and ECG information at the same time points. Table 2 presents a summary of the collection time points for PK, PD and ECG sampling:

Table 2: Time Points for PK, PD, and ECG Samples

Time relative to VELCADE administration	Cycle 1 Day 1 and Day 11 PK Sampling	Cycle 1 Day 1 and Day 11 PD Sampling	Cycle 1 Day 1[a] ECG Sampling
– 120 minutes	0	0	+
– 60 minutes	0	0	+
– 30 minutes	+	+	+
VELCADE Administration	0	0	0
+ 2 minutes	+	+	0
+ 5 minutes[b]	+	+	+
+ 15 minutes[b]	+	+	+
+ 30 minutes[b]	+	+	+
+ 60 minutes[b]	+	+	+
+120 minutes[b]	+	+	+
+240 minutes[b]	+	+	+
+360 minutes[b]	+	+	+
+600 minutes[b]	+	+	+
+ 24 hours	+	+	0
+ 48 hours	+	+	0
+ 72 hours	+	+	0

Notes: + indicated sample to be taken; 0 indicates no sample to be taken.

[a] ECG was only repeated on Cycle 1 Day 11 if there were technical concerns or clinically relevant findings on the Cycle 1 Day 1 ECG recordings

[b] Two members of the site staff were present to ensure simultaneous ECG and PK/PD sampling

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Reviewer's Comment: Bortezomib i.v. and s.c. have peak C_{max} at 2 min and 30 min, respectively. The sponsor obtained multiple and sufficient time-matched PK and ECG samples on day 1 of cycle 1 to identify bortezomib C_{max} for both administration routes. An additional ECG sample should have been obtained at 24-h post-dose to determine if bortezomib exposures had any delayed ECG effects.

4.2.6.5 Baseline

The sponsor collected and averaged three ECGs at -2, -1, and -0.5 h pre-treatment on day 1 as the study baseline.

4.2.7 ECG Collection

"Full 12-lead ECGs were reviewed in real time at the investigator site, the following variables were provided automatically: PR, QRS, QT and QTc intervals and heart rate. The ECGs were then electronically transmitted from the investigator site to the centralized ECG laboratory (b) (4)

"Each ECG underwent independent review by a cardiologist, and using the MUSE Interval Editor software the following variables were measured manually: heart rate, RR,

QT, PR, QRS and QTcB and QTcF intervals. The cardiologist also provided a clinical interpretation.

"Interval measurements were performed in a digital environment using electronic calipers. Each interval was measured as a single measurement of an averaged complex from the chosen lead (Lead II), utilizing a validated median template methodology, with a sample of at least 3-5 original complexes. The QT interval was measured using the QT tangent method."

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 24 subjects were enrolled at 3 study sites in France. Twelve subjects were randomized to receive VELCADE as an i.v. bolus (group 1) and 12 subjects received VELCADE as an s.c. injection (group 2). Four subjects (4 of 12; 33%) in the i.v. group and 5 (5 of 12; 42%) in the s.c. group completed study treatment. Eight subjects discontinued from the study, (8 of 12; 67%) in the i.v. group and 7 (7 of 12; 58%) in the s.c. group.

Table 3: Demographic and Baseline Characteristics (Study 26866138-CAN-1004: Intent-to-Treat Analysis Set)

	-------- IV ------- (N=12)	-------- SC ------- (N=12)	------ Total ------ (N=24)
Age (Years)			
N	12	12	24
Category, n (%)			
<65	9 (75)	9 (75)	18 (75)
≥65	3 (25)	3 (25)	6 (25)
Mean (SD)	60.4 (6.10)	60.4 (5.88)	60.4 (5.86)
Median	61.0	61.5	61.0
Range	(51;71)	(49;71)	(49;71)
Gender, n (%)			
N	12	12	24
Male	3 (25)	7 (58)	10 (42)
Female	9 (75)	5 (42)	14 (58)
Weight (kg)			
N	12	12	24
Mean (SD)	69.25 (12.484)	71.25 (16.499)	70.25 (14.344)
Median	72.00	67.00	69.50
Range	(50.0;88.0)	(47.0;97.0)	(47.0;97.0)
Height (cm)			
N	12	12	24
Mean (SD)	161.58 (9.681)	163.75 (9.440)	162.67 (9.416)
Median	158.50	164.00	160.00
Range	(152.0;180.0)	(145.0;176.0)	(145.0;180.0)
Body Surface Area (m^2)			
N	12	12	24
Mean (SD)	1.73 (0.188)	1.76 (0.237)	1.74 (0.210)
Median	1.70	1.73	1.72
Range	(1.4;2.1)	(1.4;2.1)	(1.4;2.1)
ECOG Performance Status, n (%)			
N	12	12	24
0: Asymptomatic	9 (75)	8 (67)	17 (71)
1: Symptomatic, Fully Ambulatory	3 (25)	4 (33)	7 (29)

ECOG = Eastern Cooperative Oncology Group
tsub01_rdm1.rtf generated by rdm1.sas.

Source: CSR, Table 6

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Summaries of ECG measurement and their changes from baseline for other ECG parameters on Day 1 are presented in Table 4. Figure 1 display the mean change of measurements from baseline for each ECG time point for QTcF. Mean changes in QTcF interval post treatment were similar between the 2 groups. In the i.v. group the range of mean change in QTcF interval was 1 to −5.6 ms. In the s.c. group the range of mean change in QTcF interval was −3.6 to −12.3 ms. No clinically relevant numerical increase in the mean QTcB or QTcF at any time point after bortezomib dosing in either of the treatment groups; actually, a negative mean change was noted at nearly every time point in both groups.

Table 4 Summaries of ECG Measurements and their Change from Baseline Over Time for QTcF on Day 1

	N	Mean	SD	Med	Min	Max	Base Mean	change from baseline N	Mean	SE	SD	Med	Min	Max
QTC INTERVAL FREDERICIA														
IV														
C1 D1 +5MIN POST	11	403.91	29.368	404.00	354.0	451.0	409.52	11	-5.61	3.955	13.117	-5.67	-26.0	24.5
C1 D1 +15MIN POST	12	407.17	27.577	407.00	352.0	452.0	409.81	12	-2.64	3.512	12.166	-4.17	-19.0	25.5
C1 D1 +30MIN POST	11	411.27	31.251	416.00	347.0	450.0	409.52	11	1.76	3.545	11.759	3.00	-12.3	23.5
C1 D1 +1H POST	12	406.67	31.061	412.00	339.0	455.0	409.81	12	-3.14	3.892	13.481	-8.83	-20.3	28.5
C1 D1 +2H POST	12	405.08	29.849	403.00	346.0	450.0	409.81	12	-4.72	3.988	13.815	-4.33	-23.0	23.5
C1 D1 +4H POST	12	408.50	28.488	408.00	362.0	453.0	409.81	12	-1.31	3.941	13.652	-0.83	-30.0	23.5
C1 D1 +6H POST	12	405.92	30.500	404.00	343.0	449.0	409.81	12	-3.89	3.446	11.939	-4.33	-27.0	16.5
C1 D1 +10H POST	8	412.88	25.085	413.50	372.0	445.0	413.77	8	-0.90	5.662	16.016	2.83	-24.0	18.5
SC														
C1 D1 +5MIN POST	12	400.33	39.387	401.00	341.0	478.0	407.67	12	-7.33	5.166	17.895	-2.33	-43.7	20.7
C1 D1 +15MIN POST	12	403.00	26.571	407.00	364.0	444.0	407.67	12	-4.67	6.105	21.149	-0.33	-62.0	24.3
C1 D1 +30MIN POST	12	403.58	40.771	402.50	351.0	500.0	407.67	12	-4.08	4.140	14.343	-3.33	-27.0	24.0
C1 D1 +1H POST	12	400.50	41.618	401.00	344.0	483.0	407.67	12	-7.17	4.238	14.681	-12.33	-24.0	19.7
C1 D1 +2H POST	12	404.08	37.140	404.00	350.0	491.0	407.67	12	-3.58	4.615	15.987	0.50	-31.7	16.0
C1 D1 +4H POST	10	390.00	29.352	398.00	333.0	432.0	402.30	10	-12.30	4.130	13.059	-7.83	-38.7	0.3
C1 D1 +6H POST	12	397.00	36.262	394.50	338.0	476.0	407.67	12	-10.67	4.779	16.555	-5.33	-55.7	5.0
C1 D1 +10H POST	10	398.70	36.975	397.00	341.0	465.0	407.17	10	-8.47	3.108	9.828	-11.00	-21.7	9.7

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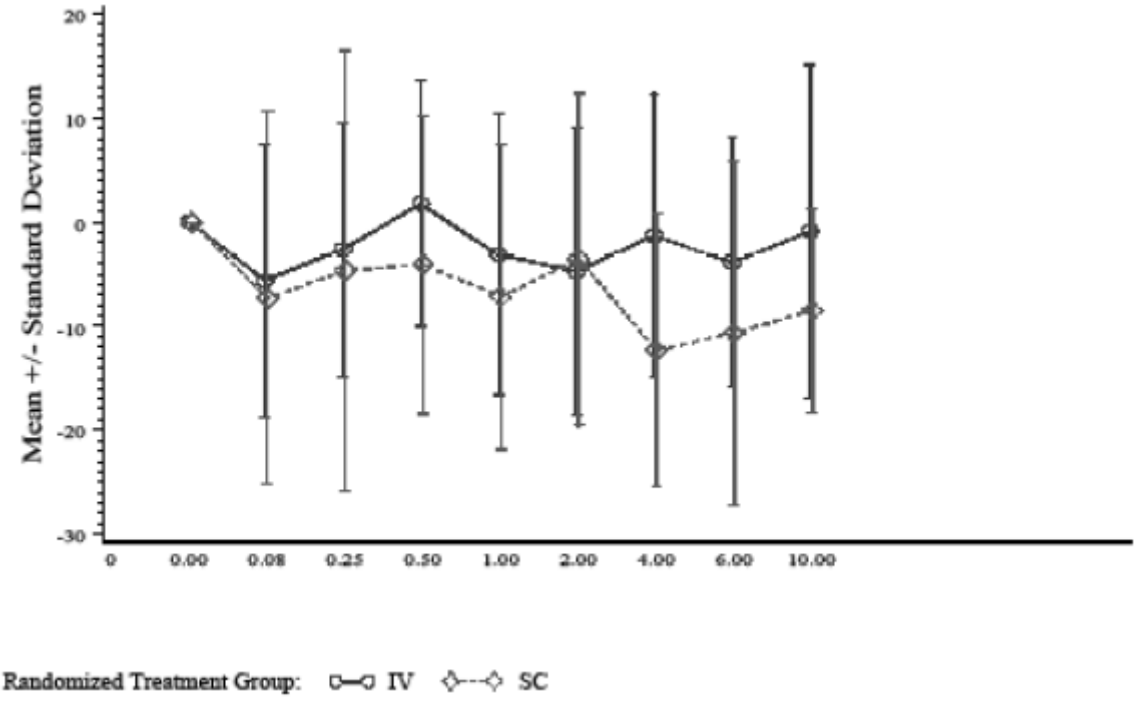
Figure 1: Mean Change (± Standard Deviation) of QTcF Change from Baseline Over Scheduled Time Points on Day 1



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Reviewer's Comments: The sponsor performed their analysis for QTcF and QTcB (not shown). Both analyses demonstrate that change from baseline QTcF and QTcB on day 1 of bortezomib treatment for both routes of administration did not result in large changes in mean QT interval (>20 ms). The study design (i.e. no positive control, no placebo,

small sample size) prohibit determination of whether bortezomib contributes to small QT prolongation effects.

4.2.8.2.2 Assay Sensitivity

Moxifloxacin was not included in this study.

Reviewer's Comments: Assay sensitivity was not demonstrated in this study as a moxifloxacin arm was not included.

4.2.8.2.3 Categorical Analysis

Eight ECGs per subject were recorded at prespecified time points during the 10 h post bortezomib administration. There was minimal change in QTcF intervals in these postdosing ECGs. No ECGs from any subject in either treatment group had increases of QTcF intervals >30 ms (Table 5).

Table 6 presents the shift from baseline to the worst QTcF interval over the 10 hr post treatment for the i.v. and s.c. treatment groups on Day 1. No subject in the i.v. treatment group had, on any ECG post treatment, a QTcF interval >500 ms or >480 to 500 ms. No subject in the s.c. treatment group had, on any ECG post treatment, a QTcF interval greater than 500 ms. One subject had a QTcF interval between >450 to 480 ms at baseline and a QTcF interval between >480 to 500 ms on at least 1 ECG after dosing.

Table 5: Shift Table of Baseline versus Worst Post Baseline Change in QTcF on Day 1

	IV (N=12)				SC (N=12)			
ECG Test	Total	Category			Total	Category		
Baseline Category	n (%)	≤30	>30 - ≤60	>60 - higher	n (%)	≤30	>30 - ≤60	>60 - higher
QT INTERVAL	12 (100)	9	3	0	12 (100)	11	1	0
0 - ≤450	11 (92)	9	2	0	12 (100)	11	1	0
>450 - ≤480	1 (8)	0	1	0	0	0	0	0
>480 - ≤500	0	0	0	0	0	0	0	0
>500 - higher	0	0	0	0	0	0	0	0
QTc INTERVAL BAZETT	12 (100)	12	0	0	12 (100)	12	0	0
0 - ≤450	12 (100)	12	0	0	9 (75)	9	0	0
>450 - ≤480	0	0	0	0	2 (17)	2	0	0
>480 - ≤500	0	0	0	0	0	0	0	0
>500 - higher	0	0	0	0	1 (8)	1	0	0
QTc INTERVAL FREDERICIA	12 (100)	12	0	0	12 (100)	12	0	0
0 - ≤450	12 (100)	12	0	0	11 (92)	11	0	0
>450 - ≤480	0	0	0	0	1 (8)	1	0	0
>480 - ≤500	0	0	0	0	0	0	0	0
>500 - higher	0	0	0	0	0	0	0	0

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Table 6: Shift Table of Baseline versus Worst Post Baseline Value in QTcF on Day 1

		IV (N=12)			
Parameter	Total	Category			
Baseline Category	n (%)	0 - ≤450	>450 - ≤480	>480 - ≤500	>500 - higher
QT INTERVAL	12 (100)	9	1	2	0
0 - ≤450	11 (92)	9	1	1	0
>450 - ≤480	1 (8)	0	0	1	0
>480 - ≤500	0	0	0	0	0
>500 - higher	0	0	0	0	0
QTc INTERVAL BAZETT	12 (100)	10	2	0	0
0 - ≤450	12 (100)	10	2	0	0
>450 - ≤480	0	0	0	0	0
>480 - ≤500	0	0	0	0	0
>500 - higher	0	0	0	0	0
QTc INTERVAL FREDERICIA	12 (100)	10	2	0	0
0 - ≤450	12 (100)	10	2	0	0
>450 - ≤480	0	0	0	0	0
>480 - ≤500	0	0	0	0	0
>500 - higher	0	0	0	0	0

		SC (N=12)			
Parameter	Total	Category			
Baseline Category	n (%)	0 - ≤450	>450 - ≤480	>480 - ≤500	>500 - higher
QT INTERVAL	12 (100)	11	1	0	0
0 - ≤450	12 (100)	11	1	0	0
>450 - ≤480	0	0	0	0	0
>480 - ≤500	0	0	0	0	0
>500 - higher	0	0	0	0	0
QTc INTERVAL BAZETT	12 (100)	8	3	0	1
0 - ≤450	9 (75)	8	1	0	0
>450 - ≤480	2 (17)	0	2	0	0
>480 - ≤500	0	0	0	0	0
>500 - higher	1 (8)	0	0	0	1
QTc INTERVAL FREDERICIA	12 (100)	11	0	1	0
0 - ≤450	11 (92)	11	0	0	0
>450 - ≤480	1 (8)	0	0	1	0
>480 - ≤500	0	0	0	0	0
>500 - higher	0	0	0	0	0

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4.2.8.3 Safety Analysis

For those subjects that discontinued study treatment the most common reason in the i.v. group was for non-hematologic toxicity Grade ≥3 (3 of 12; 25%) followed by reasons specified as 'other' (2 of 12; 17%): Grade 3 thrombopenia (1 subject [Subject 108]) and, Grade 3 atrial fibrillation and Grade 3 syncope (1 subject [Subject 103]). In the s.c. group the most common reasons for discontinuations were non-hematologic toxicity Grade ≥3 (3 of 12; 25%), disease progression (3 of 12; 25%), and a major protocol deviation (1 of 12; 8%) (administration of i.v. doses).

The safety analyses included all randomized subjects (n=24) who received at least 1 dose of study drug. All of the adverse events presented in this study report are treatment emergent.

Overall, 96% of subjects had a drug related TEAE. Twelve subjects (12 of 12; 100%) in the i.v. group and 11 of 12 (92%) subjects in the s.c. experienced at least 1 AE, all of which were considered related to VELCADE.

One subject experienced atrial fibrillation and another cardiac failure. Another subject experienced syncope.

Overall, 6 subjects (6 of 24, 25%) experienced an SAE. Five subjects (5 of 12; 42%) in the i.v. group experienced an SAE, 2 of which were considered related to VELCADE. One subject in the s.c. group (1 of 12; 8%) experienced an SAE, which was considered related to VELCADE.

There were no deaths in this study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean (SD) plasma concentration-time profiles for bortezomib for both the s.c. and i.v. routes of administration are also presented in Figure 2. PK profiles for bortezomib were similar on Day 1 and Day 11 for s.c. and i.v. administration. Also shown in Figure 2, the mean concentration values during early time-points (during absorption/distribution phases) were different between i.v. versus the s.c. routes. This difference was narrower at later time points (during the elimination phase) indicating similarity in clearances on both administration routes. A summary of bortezomib PK parameters for Day 1 and Day 11 for both routes of administration are shown in Table 7.

Four subjects (103, 224, 206 and 207), 2 from each treatment group, were not considered PK-evaluable and were excluded from the PK analyses. Subjects 103 (randomized to the i.v. group) and 224 (randomized to the s.c. group) did not complete the scheduled PK sampling on Day 11. On Day 1, blood samples from Subject 207 were taken from the same arm that the i.v. dose was administered. Subject 206 (randomized to the s.c. group) was dose reduced to 1 mg/m^2 on Day 8.

Figure 2: Mean Plasma Concentration-Time Profile for Bortezomib Following S.C. and I.V. Administration on Day 1 (left) and Day 11 (right)

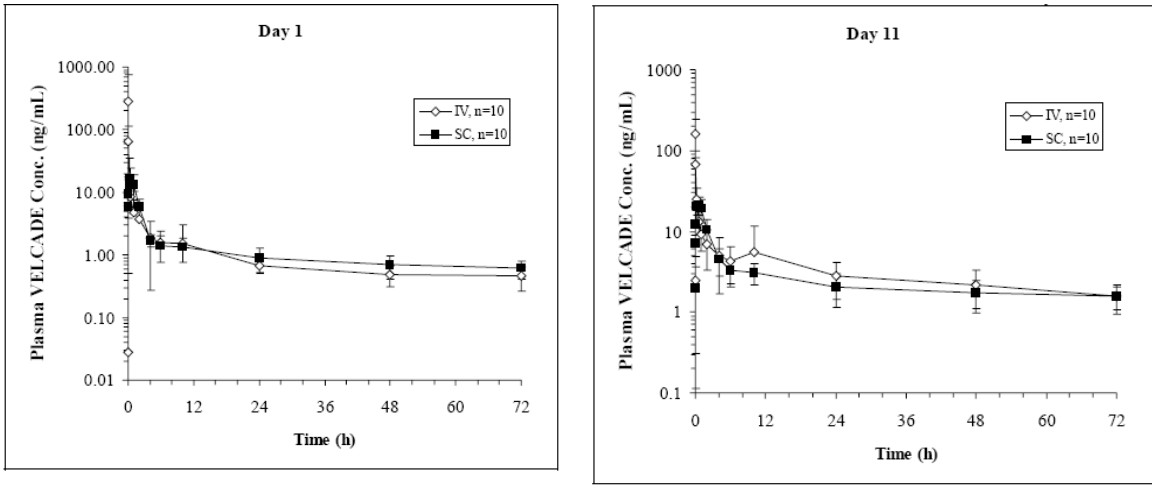

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Table 7: Mean (SD) Plasma Bortezomib Pharmacokinetic Parameters in Subjects After S.C. and I.V. Administration of Bortezomib

	Day 1		Day 11	
Parameter	IV (n=10)	SC (n=10)	IV (n=10)	SC (n=10)
t_{max} [a] (h)	0.03 (0.03-0.05)	0.53 (0.30-1.02)	0.03 (0.03-0.50)	0.50 (0.25-1.00)
C_{max} (ng/mL)	286 (466)	16.5 (8.35)	162 (79.9)	22.5 (5.36)
C_0 (ng/mL)	794 (1723)	--	321 (181)	--
AUC_{last} (ng.h/mL)	104 (99.0)	92.1 (17.8)	241 (82.0)	195 (51.2)
AUC_∞ (ng.h/mL)	183 (158)	151 (53.5)	409 (187)	405 (138)
CL (L/h)	17.9 (8.22)	--	6.60 (3.15)	--
CL/F (L/h)	--	16.6 (5.82)	--	6.22 (2.41)
Vd (L)	1636 (850)	--	538 (194)	--
Vd/F (L)	--	1330 (578)	--	765 (322)
Vd_{ss} (L)	1370 (757)	--	463 (180)	--
$t_{1/2}$ (h)	98.1 (145.0)	65.7 (46.5)	66.7 (40.7)	95.2 (52.2)
λ_z (h^{-1})	0.0173 (0.0159)	0.0157 (0.0102)	0.0139 (0.00743)	0.00909 (0.00436)

[a] Data presented as Median (Min-Max)

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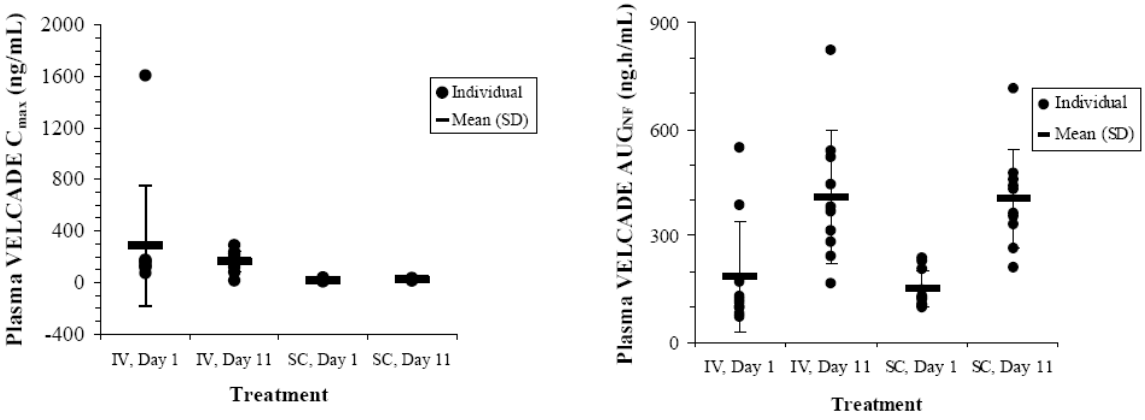
Finally, the individual and mean values of PK parameters C_{max}, AUC_∞ of each treatment group (s.c. and i.v. after Day 1 and Day 11) are graphically compared in Figure 3. The mean C_{max} values were lower for the s.c. compared with the i.v. group on Day 1 and Day 11. However, mean AUCs were similar across both the s.c. and i.v. treatment groups on Day 1 and Day 11, but showed an overall increase in AUC values on Day 11 compared to Day 1 for both treatment groups. Overall, the exposure parameters of bortezomib were similar when administered via the s.c. or i.v. routes of administration.

Figure 3: Comparison of Individual and Mean C_{max} (Left) and AUC_{∞} (Right) of Bortezomib After Both S.C. and I.V. Administrations on Day 1 and Day 11



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Reviewer's Analysis: Both routes of bortezomib administration displayed similar AUC and clearance, differing only in observed C_{max} (i.e. higher values for the i.v. treatment). The sponsor excluded 4 subjects for the PK assessment due to dose adjustments, missing PK samples from Day 11, or sampling from the same arm where the dose was administered. The reviewer included all excluded subjects except for samples from subject 207 on Day 1 (sampled from same arm as the i.v. dose) in the concentration-ΔQTcF assessment.

4.2.8.4.2 Exposure-Response Analysis

Reviewer's Analysis: Exposure-Response analysis was not performed by the sponsor. A plot of ΔQTcF vs.bortezomib concentrations is presented in Figure 6.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcB and QTcF). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals. Because of the lack of placebo data in this study design and the small number of subjects available for analysis (n=24), an individual QT correction (QTcI) was not explored.

We used the mixed model of the pooled post-dose data of QTcB and QTcF distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcB and QTcF), and the interaction term of RR and correction type. The slopes of QTcB and QTcF versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 8, it appears that QTcF had smaller absolute slopes than QTcB. Therefore, QTcF is a better correction method for the study data.

Table 8: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcB	Slope of QTcF	P_value
All	-0.0601	0.0196	(0.0001, 0.124)

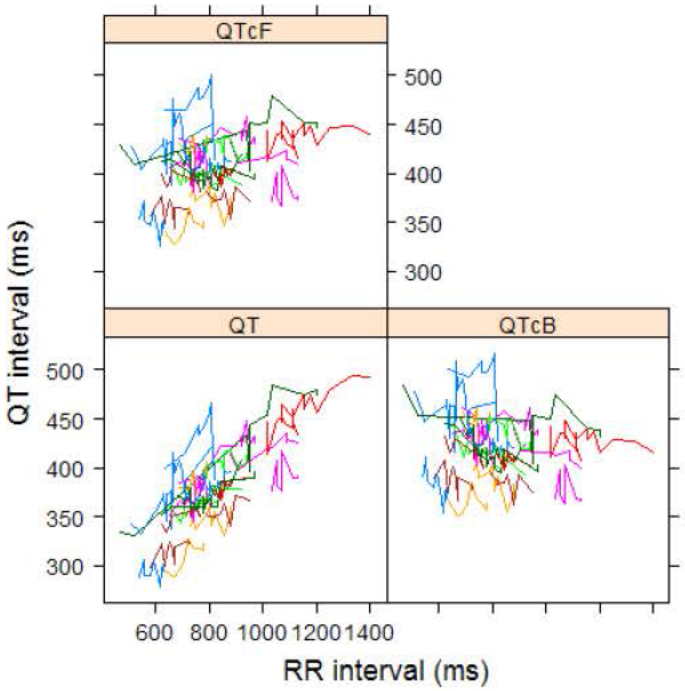
Individual slopes could not be estimated for QTcB correction method due to the high variability in the collected data and small number of subjects (n=24) on study. As such, a Mean Sum of Squared Slopes (MSSS) analysis could not be performed for all correction methods. The results for the QTcF correction are listed in Table 9. Based on these two analyses this reviewer used QTcF for the primary statistical analysis. In contrast, the sponsor performed their primary analysis using both QTcF and QTcB.

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcF	
Treatment Group	N	MSSS
All	24	0.0004

The relationship between different correction methods and RR is presented in Figure 4.

Figure 4: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTcF Analysis

5.2.1.1 The Primary Analysis for Bortezomib

The reviewer calculated the ΔQTcF time-course for the two bortezomib administration routes. The analysis results are listed in the following table.

Table 10: Analysis Results of ΔQTcF for Bortezomib 1.3 mg/m^2 S.C. and I.V.

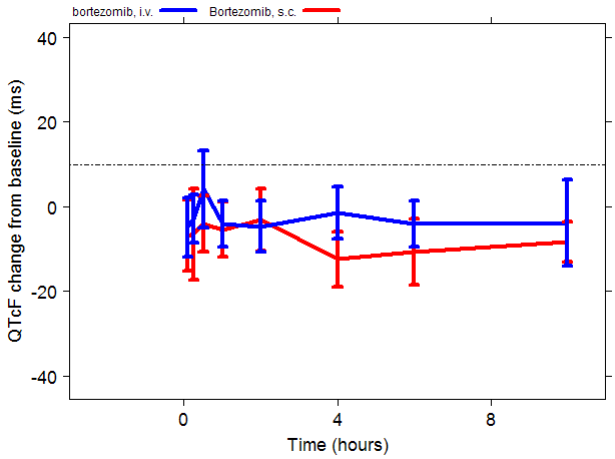
	Bortezomib 1.3 mg/m^2 s.c., Day 1			Bortezomib 1.3 mg/m^2 i.v., Day 1		
Time/(hr)	**N**	**Mean**	**90% CI**	**N**	**Mean**	**90% CI**
0.083	11	-6.8	(-15.2; 1.5)	12	-4.8	(-11 9; 2.2)
0.25	12	-6.5	(-17.3; 4.3)	12	-2.9	(-8.6; 2.9)
0.5	11	-4.1	(-10.7; 2.5)	12	4.2	(-5.0; 13.3)
1	12	-5.4	(-11.9; 1.1)	12	-4.1	(-9.5; 1.3)
2	12	-3.1	(-10.4; 4.2)	12	-4.7	(-10.7; 1.4)
4	12	-12.5	(-18.9; -6.0)	10	-1.5	(-7.7; 4.6)
6	12	-10.6	(-18.4; -2.9)	12	-4.1	(-9.5; 1.3)
10	11	-8.2	(-13.0; -3.5)	10	-3.8	(-14 1; 6.5)

The largest upper bounds of the 2-sided 90% CI for the mean change from baseline for bortezomib 1.3 mg/m^2 s.c. and bortezomib 1.3 mg/m^2 i.v. on Day 1 of treatment was 4.2 and 13.3 ms, respectively.

5.2.1.2 ΔQTcF over Time

The following figure displays the time profile of ΔQTcF for different treatment groups on Day 1. Day 1 was chosen for the primary analysis as only 4 subjects (2 from the i.v. arm and 2 from the s.c. arm) had ECG values available on Day 11 of treatment. Because of the small sample size, the results on Day 11 are not reliable.

Figure 5: Mean and 90% CI ΔQTcF Timecourse on Day 1



5.2.1.3 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are ≤450 ms, between 450 ms and 480 ms. One subject's QTcF was above 480 ms (subject ID 318, bortezomib s.c.) and reached 500 ms on day 1, 30 min post-dose.

Table 11: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value ms	
Treatment Group	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Baseline	24	65	20 (83.3%)	60 (92.3%)	4 (16.7%)	5 (7.7%)
Bortezomib 1.3 mg/m^2 s.c.	12	116	10 (83.3%)	107 (92.2%)	2 (16.7%)	9 (7.8%)
Bortezomib 1.3 mg/m^2 i.v.	12	118	10 (83.3%)	113 (95.8%)	2 (16.7%)	5 (4.2%)

Table 12 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 12: Categorical Analysis of ΔQTcF

	Total N		**Value<=30 ms**		**30 ms<Value<=60 ms**	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Bortezomib 1.3 mg/m^2 s.c.	12	118	11 (91.7%)	117 (99.2%)	1 (8.3%)	1 (0.8%)
Bortezomib 1.3 mg/m^2 i.v.	12	116	11 (91.7%)	115 (99.1%)	1 (8.3%)	1 (0.9%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 13. The largest upper limits of 90% CI for the HR mean change from baseline for bortezomib 1.3 mg/m^2 s.c. and bortezomib 1.3 mg/m^2 i.v. on Day 1 of treatment are 0.8 and 4.8 bpm, respectively.

Table 13: **Analysis Results of ΔHR for Bortezomib 1.3 mg/m^2 S.C. and I.V**

	Bortezomib 1.3 mg/m^2 s.c., Day 1			**Bortezomib 1.3 mg/m^2 i.v., Day 1**		
Time/(hr)	**N**	**Mean**	**90% CI**	**N**	**Mean**	**90% CI**
0.083	11	-1.0	(-3.2; 1.2)	12	-1.7	(-5.5; 2.1)
0.25	12	-2.5	(-5.2; 0.1)	12	-2.6	(-7.7; 2.5)
0.5	11	-4.1	(-6.9; -1.3)	12	-0.9	(-2.7; 1.0)
1	12	-4.7	(-7.0; -2.4)	12	-7.2	(-11.3; -3.0)
2	12	-3.9	(-6.5; -1.2)	12	-6.2	(-9.2; -3.3)
4	12	2.7	(-1.8; 7.2)	10	0.5	(-3.2; 4.2)
6	12	-2.9	(-5.9; 0.2)	12	-0.6	(-4.2; 3.0)
10	11	4.8	(0.0; 9.6)	10	0.8	(-3.7; 5.2)

5.2.3 PR Analysis

The outlier analysis results for PR are presented in Table 14. One subject in both bortezomib treatment arms experienced PR interval greater than 200 ms.

Table 14: Categorical Analysis for PR

	Total N		PR ≥ 200 ms	
Treatment Group	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)
Baseline	24	65	1 (4.2%)	1 (1.5%)
Bortezomib 1.3 mg/m^2 s.c.	12	116	1 (8.3%)	7 (6.0%)
Bortezomib 1.3 mg/m^2 i.v.	12	116	1 (8.3%)	3 (2.6%)

5.2.4 QRS Analysis

The outlier analysis results for QRS are presented in Table 15. One subject in both bortezomib treatment arms experienced QRS interval greater than 110 ms.

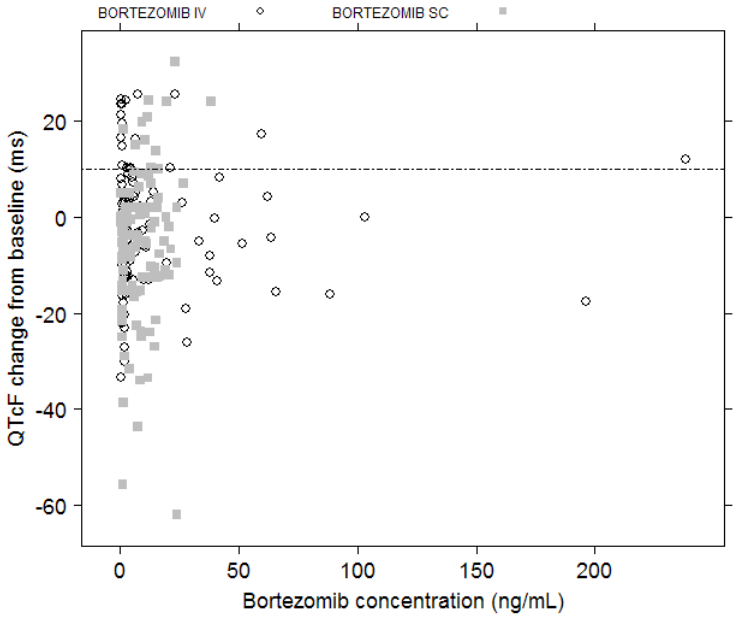
Table 15: Categorical Analysis for QRS

	Total N		QRS ≥ 110 ms	
Treatment Group	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)
Baseline	24	65	2 (8.3%)	5 (7.7%)
Bortezomib 1.3 mg/m^2 s.c.	12	116	1 (8.3%)	7 (6.0%)
Bortezomib 1.3 mg/m^2 i.v.	12	118	1 (8.3%)	8 (6.8%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔQTcF and bortezomib concentrations is visualized in Figure 6 with no evident exposure-response relationship.

Figure 6: ΔQTcF vs. Bortezomib Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

No seizure, ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 81% of the ECGs were annotated in the primary lead II, with less than 2% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	1.3 mg/m^2 administered subcutaneously (SC) or intravenously (IV) twice weekly: on Days 1, 4, 8 and 11 of 21-day treatment cycles.	
Maximum tolerated dose	1.3mg/m^2/dose administered intravenously twice a week in patients with advanced solid tumors [Reference: Protocol 98-104A]	
Principal adverse events	Most common adverse events include: asthenic conditions, nausea, diarrhea, constipation, peripheral neuropathy, thrombocytopenia, appetite decreased, pyrexia, vomiting, anemia, edema, paresthesia & dysesthesia, headache, dyspnea, cough, & insomnia [reference: USPI Table 8; Most Commonly Reported ->./=20% Adverse Events in Integrated Analyses of Relapsed Multiple Myeloma and Mantle Cell Lymphoma Studies Using 1.3mg/m^2 Dose Administered IV] Dose limiting adverse events at 1.56mg/m^2/dose administered IV twice weekly were diarrhea & sensory neuropathy in patients with advanced solid tumors [Reference: Protocol 98-104A] Dose limiting adverse events at doses at 1.2 and 1.38 mg/m^2 administered IV twice weekly were, hyponatremia, hypokalemia, , and malaise in patients with refractory hematologic malignancies [Reference: Protocol LCCC 9834/MSKCC 00-31]	
Maximum dose tested	Single Dose	2.0 mg/m^2 administered IV weekly in patients with advanced solid tumors [Reference: Protocol DM98-194]
	Multiple Dose	1.56 mg/m^2/dose administered IV twice a week for 2 consecutive weeks (on Days 1, 4, 8, and 11) followed by a 10-day rest period in patients with advanced solid tumors.[Reference: Protocol 98-104A]
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC **IV**: Highest dose with single dose PK data is 2 mg/m^2 in Study DM98-194 where mean (%CV) C_{max} was *36 ng/mL (67%) and mean (%CV) AUC_{0-inf} was 77 ng.hr/mL (36%). At 1.3 mg/m^2 (prescribed starting dose), the mean (%CV) single dose C_{max} is 286 ng/mL (163%) and AUC_{0-inf} is 183 ng.hr/mL (86%) in Study CAN1004. **SC**: Highest dose with single dose PK data is 1.3 mg/m^2 in Study CAN1004 where mean (%CV) C_{max} was 16.5 ng/mL (51%) and mean (%CV) AUC_{0-inf} was 151 ng.hr/mL (35%). * Lower reported Cmax in this study may in

		part be related to different PK sampling scheme.
	Multiple Dose	Mean (%CV) Cmax and AUC Highest dose with multiple dose PK data available is 1.3 mg/m^2 administered SC or IV in twice weekly schedule. Since both routes were studied in Study MMY3021, PK parameters from this study on Day 11 of Cycle 1 are provided below: **IV**: Mean C_{max} 223 ng/mL (CV 45%); mean $AUC_{0\text{-last}}$ 151 ng.hr/mL (CV 28%). **SC**: Mean C_{max} 20.4 ng/mL (CV 43%); mean $AUC_{0\text{-last}}$ 155 ng.hr/mL (CV 37%).
Range of linear PK	Based on the results of noncompartmental analyses of PK data following IV bolus dosing, there is no indication of dose-related nonlinearity in bortezomib exposure, although plasma clearance is decreased following multiple dose administration on a twice weekly dosing schedule. **Plasma Clearance vs. Dose**: Study DM98-194 evaluated bortezomib single dose PK following IV bolus administration. Clearance was similar within the evaluated dose range of 1.45 to 2.0 mg/m^2. Study M34103-058 evaluated PK following twice weekly IV bolus dosing (on Days 1, 4, 8, 11 of 21-day cycles) at 1.0 and 1.3 mg/m^2. Clearance was similar across the 1.0 mg/m^2 and 1.3 mg/m^2 doses studied. **Plasma Clearance vs. Time**: Time-dependency in bortezomib plasma clearance has been noted following twice weekly dosing. In Study M34103-058, the mean total body plasma clearance values were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and were reduced ranging from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively.	
Accumulation at steady state	**SC route**: In Study CAN-1004, following administration on a twice weekly dosing schedule, mean $AUC_{0\text{-last}}$ following administration of the Day 11 dose of Cycle 1 was 2.1 times the mean $AUC_{0\text{-last}}$ following administration of the Day 1 dose of Cycle 1, indicating an approximately *2.1-fold accumulation. **IV route**: In StudyM34103-058, following administration on a twice weekly dosing schedule, mean $AUC_{0\text{-48hr}}$ following administration of the Day 11 dose of Cycle 1 was 2.4 times the mean $AUC_{0\text{-48hr}}$ following administration of the Day 1 dose of Cycle 1, indicating an approximately *2.4-fold accumulation. *accumulation ratios estimated from mean AUC data on Days 1 and 11; so no CV could be reliably estimated	
Metabolites	The major metabolic pathway is deboronation to form 2	

		following twice weekly repeat dose administration (%CV: 51%-92%)
Intrinsic Factors	Age	Formal analyses have not been performed
	Sex	Formal analyses have not been performed
	Race	Formal analyses have not been performed
	Hepatic & Renal Impairment	**Mild Hepatic impairment**: No effect on bortezomib PK. **Moderate/ Severe Hepatic Impairment**: 1.6-fold increase in dose-normalized AUC (geometric mean ratio relative to normal hepatic function); no readily apparent effect on C_{max}. **Renal impairment**: No effect of any degree of renal impairment (including patients on dialysis) on bortezomib PK.
Extrinsic Factors	Drug interactions	**Ketoconazole**: 1.35-fold increase in AUC, no readily apparent effect on C_{max}. **Omeprazole**: No effect on C_{max} or AUC. **Rifampin**: 45% decrease in AUC; 23% decrease in C_{max}. **Dexamethasone**: No effect on AUC; No readily apparent effect on C_{max}.
	Food Effects	Not applicable as parenteral administration
Expected High Clinical Exposure Scenario	**Co-administration with strong CYP3A inhibitors:** In a ketoconazole DDI study of IV bortezomib, a 1.35-fold increase in AUC (geometric mean ratio) was observed with a 90% CI of 1.032–1.772 -fold. There was no readily apparent effect of ketoconazole on bortezomib C_{max}. The observed 1.35-fold-increase in AUC of IV bortezomib by ketoconazole is expected to be translatable to the setting of SC dosing as bioavailability is complete following SC dosing. **Moderate or Severe Hepatic Impairment (HI):** In a study of the effect of varying grades of HI on the PK of IV bortezomib, a 1.58-fold increase in AUC (geometric mean ratio) was observed with a 90% CI of 1.172 - 2.131 -fold. There was no readily apparent effect of HI on bortezomib C_{max}. The observed increase in AUC of IV bortezomib in moderate or severe HI is expected to be translatable to the setting of SC dosing as bioavailability is complete following SC dosing. Based on results of the HI study, the USPI-recommended starting dose for patients with moderate or severe HI is 0.7 mg/m^2 (vs. 1.3 mg/m^2 in the general patient population). Therefore, when administered to patients with moderate or severe HI as per the dose modification guidelines in the USPI, the exposures of bortezomib would not be expected to be higher than those observed in the general patient population at the full recommended starting dose of 1.3 mg/m^2.	

	deboronated metabolites (M1 and M2) that subsequently undergo hydroxylation to several metabolites. Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after IV administration of VELCADE from Phase 1 Study DM98-194 indicate that the plasma levels of metabolites are low compared to the parent drug.	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) For SC administration, absolute bioavailability estimated in Study MMY3021 is *0.992 (90% CI: 0.8018, 1.2280) *parallel group design, hence CV not estimated
	Tmax	• Median (range) for parent **SC dosing**: Median T_{max} observed in Study MMY3021 is 0.50 hours (range: 0.08-1.00 hours). • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV) $V_{d,\beta}$ (terminal phase volume of distribution) following single or repeat dose administration at 1.3 mg/m^2 in Study M34103-058 was 2015-2505 liters (%CV: 60%-148% across days of measurement).
	% bound	Mean (%CV) 83%
Elimination	Route	• Primary route; percent dose eliminated Mass balance study not conducted. Metabolism expected to be the major route of clearance. • Other routes
	Terminal t½	• Mean (%CV) for parent 11.5-30.7 hours (%CV: 110%-146%) following first dose of Cycle 1; 75.6-193 hours (%CV: 60%-88%) following twice weekly repeat dosing. • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV) **CL**: 102-112 L/hr (%CV: 47%-66%) following first dose of Cycle 1; 15-32 L

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAO ZHU
10/13/2011

JEFFRY FLORIAN
10/13/2011

MONICA L FISZMAN
10/13/2011

NORMAN L STOCKBRIDGE
10/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021602Orig1s027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021602 SUPPL # SE2-027 HFD # 160

Trade Name Velcade

Generic Name bortezomib

Applicant Name Millennium

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021602 Velcade

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

MMY-3021

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

MMY-3021

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 056515	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Amy Baird
Title: Regulatory Project Manager
Date: January 20, 2012

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
01/23/2012

EDVARDAS KAMINSKAS
01/23/2012

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 021602 | Supplement Number: 027 | NDA Supplement Type (e.g. SE5): SE2

Division Name: DHP | PDUFA Goal Date: 1/23/2012 | Stamp Date: 3/23/2011

Proprietary Name: Velcade

Established/Generic Name: bortezomib

Dosage Form: Injection

Applicant/Sponsor: Millennium Pharmaceuticals

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 0
(Attach a completed Pediatric Page for each indication in current application.)

Indication: _____

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☐ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed$^{\Delta}$
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND *(2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
01/23/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 021602 BLA#	NDA Supplement #:S- 027 BLA STN #	Efficacy Supplement Type SE- 2
Proprietary Name: VELCADE Established/Proper Name: bortezomib Dosage Form: Injection Strengths:		
Applicant: Millennium Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 3/23/11 Date of Receipt: 3/23/11 Date clock started after UN:		
PDUFA Goal Date:	Action Goal Date (if different):	
Filing Date: 5/22/11	Date of Filing Meeting: 5/12/11	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Subcutaneous route of administration as an alternative to the existing intravenous ROA.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***				
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***				
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	This is a fully electronic submission

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 12, 2011

BLA/NDA/Supp #: 021602/S-027

PROPRIETARY NAME: VELCADE

ESTABLISHED/PROPER NAME: bortezomib

DOSAGE FORM/STRENGTH: Injection

APPLICANT: Millennium Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): addition of a subcutaneous route of administration (ROA) as an alternative to the existing intravenous ROA

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	AmyBaird	Y
	CPMS/TL:	Janet Jamison	Y
Cross-Discipline Team Leader (CDTL)	Julie Bullock, PhD		Y
Clinical	Reviewer:	Firoozeh Alvandi, MD	Y
	TL:	Virginia Kwitkowski	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Young Jin Moon, PhD	Y
	TL:	Julie Bullock, PhD	Y
Biostatistics	Reviewer:	Qing Xu, PhD	Y
	TL:	Mark Rothmann, PhD	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen, PhD	Y
	TL:	Haleh Saber, PhD	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Zedong Dong, PhD	N
	TL:	Janice Brown, PhD	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☐ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
01/19/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, December 14, 2011 4:07 PM
To: 'Visiers, Irache'; 'Bedell, Eileen'
Subject: FW: NDA 021602/S-027 Velcade - FDA Clinical Request for Information

Eileen and Irache,

Please disregard my previous email from today at 1:22pm regarding NDA 021602/S-027. Instead, please see below where I have attempted to clarify our original request.

Please refer to your supplemental NDA application for NDA 021602/S-027 Velcade dated March 23, 2011, which provides for subcutaneous route of administration (ROA) as an alternative to the existing intravenous ROA.

Per the request of the FDA review team, please provide a response to the following:

Given the results of the usability testing study submitted with S-027, conducted by (b) (4) demonstrating that 14 out of 45 participants (31%) committed at least one error during preparation of Velcade for administration, we are requesting that you propose your plans to enhance the accuracy of Velcade reconstitution and preparation in the community. Please attempt to provide a response NLT December 23, 2011.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Baird, Amy
Sent: Wednesday, December 14, 2011 1:22 PM
To: 'Bedell, Eileen'; 'Visiers, Irache'
Subject: NDA 021602/S-027 Velcade - FDA Clinical Request for Information

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Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager

Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
12/14/2011

Baird, Amy

From: Baird, Amy
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Subject: NDA 021602/S-027 Velcade - FDA Clinical Request for Information

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Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
12/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff**

E-mail to: **CDER OPS IO MICRO**

Paper mail to: **WO Bldg 51, Room 4193**

FROM: Zedong Dong

PROJECT MANAGER *(if other than sender):Scott N. Goldie*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
19 October 2011		21602 S027	CMC PAS Supplement	23 March 2011

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE
Velcade (bortezomib) injection 3.5 mg	Standard	23 January 2012	23 December 2011

NAME OF APPLICANT OR SPONSOR: Millennium Pharmaceuticals, Inc.

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: _____
- ☐ BUNDLED
- ■ DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS:

I am writing to follow up with you on this. I would like to have the micro folks take a quick look, whether they are fine with the data. if they need additional data, we should send the information request as early as possible. thanks.

The above is an efficacy supplement with a goal date of 01/23/2012. We would like the micro folks to take a look at it regarding the propsoed maximum storage duration of 8 hours for the reconstituted DP at 25 deg C and indoor lighting. Thanks.

SIGNATURE OF REQUESTER

REVIEW REQUEST DELIVERED BY (Check one):

■ DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

■ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

SCOTT N GOLDIE
10/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE (Attention: Sue Kang)**			FROM: Amy Baird, Regulatory Project Manager, Division of Hematology Products	
DATE 9-28-2011	IND NO.	NDA NO. 021602/S-027	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT 3/23/2011
NAME OF DRUG Velcade (bortezomib) for Injection	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 12/19/2011

NAME OF FIRM: Talon Therapeutics

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Requesting OSE review of labeling associated with this Supplemental New Drug Application which provides for the addition of subcutaneous route of administration as an alternative to the existing intravenous IV route of administration..

We ask that OSE attend all pertinent review meetings (labeling, team meetings).

MOR= Dr. Firoozeh Alvandi
RPM= Amy Baird

EDR link is below

\\CDSESUB1\EVSPROD\NDA021602\0046

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

AMY C BAIRD
09/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-DDMAC-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Amy Baird, Regulatory Project Manager, Division of Hematology Products, 301-796-4969

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
9-29-2011		021602/S-027	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Velcade (bortezomib) for Injection			12/19/2011

NAME OF FIRM:	
Millennium Pharmaceuticals	PDUFA Date: 1/23/2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ✓ PACKAGE INSERT (PI)
- ✓ PATIENT PACKAGE INSERT (PPI)
- ✓ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ✓ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ✓ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: 11/7/2011, 11/9/2011, 11/14/2011, 11/17/2011, 11/23/2011, 12/1/2011, 12/15/2011, 12/19/2011

Below is the EDR link to the original submission:
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/s/

AMY C BAIRD
09/29/2011

Baird, Amy

From: Baird, Amy
Sent: Thursday, September 15, 2011 10:27 AM
To: 'Visiers, Irache'; Bedell, Eileen
Subject: NDA 021602/S-027 Velcade - FDA Clinical Information Request

Irache,

Please refer to your supplemental NDA application for NDA 021602/S-027 Velcade dated March 23, 2011, which provides for subcutaneous route of administration (ROA) as an alternative to the existing intravenous ROA.

Please provide an algorithm for the disposition of all patients randomized, and clearly specify the number of patients (subjects) per treatment arm that constitute the following analysis populations, 1) ITT (intent to treat), 2) Response evaluable population for efficacy, and 3)Safety population, accounting for any and all discrepancies among the numbers of subjects as compared to the number of patients constituting the ITT.
Please be sure to include in your response a justification for including 147 subjects in the SC arm for some analyses and 145 subjects in the SC arm for other analyses.

Also, please provide a data set that includes response information for the ITT population only.

Please provide a response to these requests by COB Tuesday, September 20, 2011.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
09/15/2011

Baird, Amy

From: Baird, Amy
Sent: Friday, August 26, 2011 7:41 PM
To: 'Visiers, Irache'
Subject: NDA 021602/S-027 Velcade - Request for Information

Attachments: HighlightsofClinicalPharmacology (2).doc

Irache,

Please refer to your supplemental NDA application for NDA 021602/S-027 Velcade dated March 23, 2011, which provides for subcutaneous route of administration (ROA) as an alternative to the existing intravenous ROA.

The Division of Cardio Renal Products is reviewing the study entitled "Comparison of Pharmacokinetics and Pharmacodynamics of Subcutaneous Versus Intravenous Administration of Bortezomib in Patients With Multiple Myeloma."

In order for the Division to complete their review the attached Highlights of Clinical Pharmacology table must be completed and submitted. Also, please submit all study related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com

HighlightsofClinicalPharmacolo...

Please do not hesitate to contact me should you have any questions.

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: QT/IRT Team Interdisciplinary Review Team
Attention: Devi Kozeli

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Amy Baird, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8-18-2011		021602	S-027	3-23-2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Velcade (bortezomib) for Injection			10-11-2011

NAME OF FIRM: Millennium Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The sponsor submitted supplement 27 to the NDA March 23, 2011 The Protocol is #26866138-CAN-1004 entitled, "Comparison of pharmacokinetics and pharmacodynamics of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma " The primary objective was to characterize the pharmacokinetics (PK) of the two routes of administration The secondary objectives were to characterize the pharmacodynamics (PD) (whole blood 20S proteasome inhibition), safety (including cardiac safety), and efficacy of the two routes of administration

This trial was an open label, randomized, phase 1 study of subjects with symptomatic multiple myeloma (MM) after at least 1 prior therapy Subjects were to be randomized without stratification to receive VELCADE either as an intravenous (i v) bolus (group 1) or as a subcutaneous (s c) injection (group 2) VELCADE was administered at a dose of 1 3 mg/m2 of body-surface area twice weekly for 2 weeks (on Days 1, 4, 8, and 11), followed by a 10-day rest period (Days 12 to 21) without treatment, for up to 8 cycles 24 subjects were enrolled and analyzed in the study (12 in each group) *See next page*

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Central ECG evaluation:
ECGs were read at a centralized ECG data center (b) (4) The MUSE Interval Editor software, was used to provide the following variables: RR, PR, QRS, QT and QTc intervals (both QTcF and QRcB) and heart rate. The QT interval was measured using the QT tangent method. Twelve-lead electrocardiograms (ECGs) were recorded at screening (to determine subjects eligibility) and in Cycle 1 on Day 1 at the following 11 time points: predose: 2h, 1h, 0.5h prior to study drug administration, and postdose: 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, and 10 hours. There was the provision to record an additional set of 11 ECGs in Cycle 1 on Day 11 (at the same time points as performed on Day 1) if deemed necessary by the investigator.

ECG Analysis:
Each ECG parameter was summarized as the mean (±standard deviation) change from baseline for each time point (5 min, 15 min, 30 min, 60 min, 2h, 4h, 6h and 10h post VELCADE administration) for each treatment group on Day 1. Figures are also provided for the mean change from baseline for QT, QTcF and QTcB over time for both treatment groups. In addition, frequency tables of significant abnormal values and changes from baseline in each ECG parameter are also provided for each treatment group on Day 1, and in separate table, by gender. Shift tables of baseline QT, QTCB and QTCF values versus the worst post baseline value and mean change in value for each treatment group on Day 1 are provided. By-subject listings of QT, QTCB and QTCF over time are also provided.

Below is the EDR link to NDA 021602/S-027

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Clinical Reviewer: Karen McGinn, M.D.
Clinical Pharmacology Reviewer: Young Jin Moon, Ph.D.
RPM: Amy Baird

Also, attached is a review completed by the FDA Office of Surveillance and Epidemiology regarding Bortezomib and Prolonged QT Interval.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Bortezomib and Prolonged QT Interval

Date:	6/15/2011
Reviewer(s):	Katherine Coyle, Pharm.D., BCOP Safety Evaluator, Division of Pharmacovigilance II (DPV II)
Team Leader:	Robert Pratt, Pharm.D. Team Leader, Division of Pharmacovigilance II
(Deputy) Division Director:	Bindi Nikhar, M. D. Division of Pharmacovigilance II
Drug Name(s):	Bortezomib (Velcade)
Application Type/Number:	021602
Submission Number:	(b) (4)
Applicant/sponsor:	Millennium Pharmaceuticals, Inc.
OSE RCM #:	2011-1132

CONTENTS

EXECUTIVE SUMMARY

This review evaluates postmarketing reports of QT prolongation associated with bortezomib (Velcade) to inform the Division of Drug Oncology Products (DDOP) of need for further evaluation of an already existing warning regarding QT prolongation in the Warning and Precautions section of the label. The label currently states that there have been isolated cases of QT interval prolongation in clinical studies and that causality has not been established. In addition, Torsades de Pointes and ventricular tachycardia are mentioned under Adverse Events from clinical studies. Of the162 reports of QT interval prolongation evaluated from the Adverse Event Reporting System (AERS), 21 met the case definition. Bortezomib was found to have possible causality in 13 cases, though each case reported additional risk factors such as electrolyte imbalances, underlying heart disease, and concurrent administration of drugs known to cause QT prolongation. Four cases with possible causality resulted in death but the deaths were not attributed to bortezomib. Non-clinical data suggest cardiovascular toxicity with bortezomib, including QT interval prolongation; it is not entirely clear how doses used in animal studies relate to human use.

Based on the above, it appears that use of bortezomib may be associated with QT interval prolongation. However, given the limitations of AERS data, and concerns that this risk has not been fully evaluated, it is recommended that DDOP consider further evaluation of QT prolongation in patients receiving bortezomib.

1 INTRODUCTION

1.1 BACKGROUND

This Division of Pharmacovigilance II review is in response to a request from the Office of Oncology Drug Products to review the Adverse Events Reporting System (AERS) database for post-marketing reports of QT prolongation associated with bortezomib (Velcade). The sponsor, Millennium Pharmaceuticals, Inc., recently (b) (4) The label contains only limited QT prolongation data from the clinical trials and animal studies. Therefore, a request was made for a search of post-marketing reports of bortezomib and adverse cardiac events related to QT prolongation.

1.2 REGULATORY HISTORY

Bortezomib, a proteasome inhibitor, was approved on May 13, 2003 and initially indicated for the treatment of multiple myeloma in patients who have received at least two prior therapies and have demonstrated disease progression. Since that time, the indication for bortezomib has expanded to include front-line treatment for multiple myeloma and treatment of mantle cell lymphoma in patients who have received at least one prior therapy. Bortezomib is dosed at 1.3 mg/m^2 as an IV bolus injection with a dosage regimen that varies based on indication and use of a combination regimen.

1.3 PRODUCT LABELING

The original bortezomib label contained no information regarding QT prolongation. A modification was made to the label in March 2005 that referenced isolated cases of QT prolongation reported in clinical studies. Additionally, Torsades de Pointes was added to the Cardiac Disorders section of Serious Adverse Events from Clinical Studies and Post-marketing.[1] In May of 2006, labeling changes were made to include QT prolongation found in animal studies.

[1] This information was based on reports submitted by the sponsor. A separate review of these reports was not performed under the NDA (personal communication, Robert Kane, Medical Officer, Division of Hematology Products,).

Current labeling for bortezomib includes the following information regarding QT prolongation:

- Cardiac Disorders (5.4) in the **Warning and Precautions:** *There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.*
- Clinical Trial Safety Information in **Adverse Events** (6.1): *Cardiac disorders: Torsades de pointes*
- **Overdose** (10): *Studies in monkeys and dogs showed that IV bortezomib doses as low as 2 times the recommended clinical dose on a mg/m^2 basis were associated with increases in heart rate, decreases in contractility, hypotension, and death. In dog studies, a slight increase in the corrected QT interval was observed at doses resulting in death.*
- **Nonclinical Toxicology:** (13.2): Cardiovascular Toxicity: Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses ≥1.2 mg/m^2 induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Other relevant cardiac labeling can be found in Appendix A.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

The QT interval represents the duration of ventricular depolarization and repolarization and is measured on the electrocardiogram (ECG). When the QT interval is corrected for the heart rate, it is referred to as the QTc. The definition of a prolonged QT interval can change based on several variables. For this reason, cases were included in this review if the report contained the term torsades de pointes or QT/QTc prolongation, regardless of whether ECG results were reported.

Cases of QT prolongation were evaluated for a causal relationship to bortezomib and categorized as unassessable, unlikely, possible, or likely based on the information in the AERS reports. Table 1 describes how the categories were defined based on the WHO-Causality Categories.

Table 1: Causality Categorization and Definitions

Causality term	**Assessment criteria**
Unassessable	Case contained an adverse event that cannot be evaluated due to insufficient or contradictory information
Unlikely	Case contained an adverse event that is associated with the drug but time to drug intake is improbable or event may be explained by disease or other drugs
Possible	Case contained an adverse event with a time to drug intake that is probable but event may be explained by disease or other drugs
Likely	Case contained an adverse event with a time to drug intake that is probable and event is unlikely to be attributed to disease or other drugs

2.2 AERS Selection of Cases

We searched the Adverse Event Reporting System (AERS) database using the strategy in Table 1.

Table 1: AERS Search Strategy	
Date	April 6, 2011
Time period	Approval May 13, 2003 – April 6, 2011
Drug Names	Bortezomib, Velcade
MedDRA Search Strategy	Torsade de Pointes/QT prolongation (Narrow SMQ). For the comprehensive list of terms in this query see Appendix B

The consultation from OODP requested that the search include adverse events related to QT prolongation including sudden death. Therefore the following terms were added to the Torsades de pointes/QT prolongation Narrow SMQ: cardiac arrest, sudden cardiac death, ventricular arrhythmias, ventricular fibrillation, and ventricular flutter.

3 RESULTS

3.1 AERS Cases

The AERS search resulted in 162 reports. Each report was reviewed, duplicates were identified and the QT/QTc prolongation case definition was applied. All reports of Torsades de Pointes also contained the term QT prolongation, therefore this review will reference all such cases as QT prolongation.

141 cases were not included in the final analysis for the following reasons:

- Duplicate reports (16)
- Did not meet case definition (125); reported cardiac events that did not specify QT prolongation.

The remaining 21 cases were further analyzed. A list of case numbers and corresponding manufacturer control numbers can be found in Appendix C.

Demographic and other information on the 21 cases are summarized in Table 2.

Table 2: Cases reporting QT/QTc prolongation received by FDA from 5/13/03 to 4/6/11.			
Demographic data for all cases (n=21)			
Age (years)	Mean 60	Median 65	Range 6-80
Gender	Male 8	Female 10	Unknown 3
Year of FDA Receipt	2004-2010		
Country of occurrence	United States 16	Foreign 5	
Report Type	15-day 20	Periodic 1	
Causality	Possible 15	Unlikely 4	Unassessable 2
Rechallenge	Negative 3	Unknown 18	

Data for cases with possible causality (n=13)			
Outcome	Death 4 Hospitalized 3	Life-Threatening 3	Other Serious 3
Indication for Use	Multiple Myeloma 9	Acute Myeloid Leukemia 4	
Electrolyte Imbalance	Yes 3	No 1	Unknown 9
Concomitant use of QT prolonging agent	Yes 13		
Underlying heart disease	Yes 4	No 4	Unknown 5
Time from Velcade dose to event	0-13 Days 8	$\geq$ 14 Days 3	Unknown 2

4 DISCUSSION

Drug induced QT interval prolongation is a well known and potentially life threatening adverse event. When evaluating drugs for this adverse event, it is important to consider risk factors that may predispose patients to this arrhythmia. Major risk factors for QT prolongation include electrolyte imbalances, underlying heart disease, and concurrent administration of drugs known to cause QT prolongation.

In this review, 125 of the 162 AERS cases identified by our search strategy did not meet the case definition. Cases that contained terms related to ventricular arrhythmias but did not report QT prolongation were excluded. All six reports of sudden death were also excluded, as these occurred outside of the hospital where patients had no ECG monitoring; no information regarding QT prolongation was reported.

Of the 21 cases that met the case definition, 13 cases were classified as possibly caused by bortezomib. An additional 3 cases were considered unlikely caused by bortezomib, and 5 cases were unassessable. Bortezomib cases were classified as having possible causality if the report indicated one or more risk factors were present at the time of QT prolongation. All of the 13 cases assigned possible causality reported concomitant use of medications that have independently demonstrated QT prolongation. These medications included antiarrhythmics, antimicrobials, antiemetics, antipsychotics, as well as some miscellaneous agents. Additional risk factors found in these cases included underlying heart disease and electrolyte imbalance. Underlying heart disease, consisting of heart block, cardiac stenosis, and a history of arrhythmias was found in 4 of the possible cases. An electrolyte imbalance referring to hypomagnesemia, hypokalemia, or hypocalcemia, was noted in 3 of the possible cases. One other case reported increased intracerebral pressure, which is also a risk factor for QT prolongation.

Another variable considered was time from bortezomib administration to QT prolongation. However, this was difficult to assess. In all of the possible cases, patients were receiving concomitant medications and the time from administration of these to development of QT prolongation was not reported. Furthermore, ECGs were often done either monthly or if a patient was symptomatic. It is possible that patients may have had asymptomatic QT prolongation that went unnoticed until a monthly ECG was done. Therefore, assessment of the temporal relationship did not provide much insight into the association of bortezomib and QT prolongation.

Four cases with possible drug-adverse event causality resulted in death. However, the causality of death was not attributed to bortezomib in the case reports. Deaths were reportedly due to disease progression, intracerebral bleed, myocardial infarction unrelated to bortezomib, and a pulmonary thromboembolism that occurred prior to the initiation of bortezomib.

Cases of QT prolongation were classified as unlikely related to bortezomib if the QT interval did not correct itself after discontinuation of bortezomib, or if the QT prolongation was corrected with electrolyte replacement. Cases were classified as unassessable if there was insufficient information regarding bortezomib administration.

The proposed mechanism for bortezomib to cause QT prolongation is unknown. It has been reported that most drugs causing QT prolongation act by binding to the HERG ion channel.[2] If a drug interferes with this channel, then potassium inflow to myocardial cells decreases resulting in prolongation of repolarization and QT prolongation. An association between bortezomib and the HERG ion channel, or any other method known to cause QT prolongation, is not clear.

Nonclinical studies mention that bortezomib has been shown to distribute to most tissues in the body, including the myocardium. Animal studies have suggested that bortezomib may have an effect on the QT interval at increasing doses. In isolated guinea pig hearts, significant lengthening of the QT interval was seen at higher doses of bortezomib when compared to vehicle control. However, the effect was no longer seen when the QT interval was corrected for heart rate (QTc)[3]. The bortezomib label reports dog studies showed a slight increase in QTc interval at bortezomib doses resulting in death.[4] It is not entirely clear how doses used in animal studies relate to human doses. Further elaboration of the effect of bortezomib in prolonging QT interval in humans would be helpful in assessing this adverse event.

There were several limitations to the information collected in this review. Many cases did not report ECG results therefore a prolonged QT interval could not be confirmed. Additionally, since many cases did not have baseline and follow up ECG reports, it could not be established in most cases when QT prolongation began in relation to the patient receiving bortezomib. Furthermore, many cases did not contain information about risk factors, such as electrolytes or underlying cardiac disease.

5 CONCLUSIONS

In this review of bortezomib, all cases of QT prolongation with possible causality had risk factors that may have predisposed patients to developing QT prolongation. These risk factors include electrolyte imbalances, underlying heart disease, and concurrent administration of drugs known to cause QT prolongation. While causality could not be fully established, based on reports of QT prolongation with bortezomib in animal studies, isolated cases in clinical trials, as well as reports in this review, it does appear that use of use of bortezomib may be associated with QT interval prolongation . .

6 RECOMMENDATIONS

At this time, DPV II recommends considering further clinical testing of QT prolongation in patients receiving bortezomib.

[2] Moss AJ. Drug-Induced QT Prolongation: An Update. Ann Noninvasive Electrocardiol. 2006 Jan;11(1):1-2.

[3] Velcade Pharmacology/Toxicology consult Memorandum dated 4/5/04. NDA 21602 DHHS/PHS/FDA/CDER/Division of Cardio-Renal Drug Products. Accessed 4/7/11.
http://darrts fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=2601420&fromHistoryPage=true&appPk=114417

[4] Velcade labeling. NDA 21602. Access 5/16/11 http://www.accessdata fda.gov/drugsatfda_docs/label/2010/021602s023lbl.pdf

APPENDICES

APPENDIX A. BORTEZOMIB LABELING OF CARDIAC EVENTS

5 WARNINGS AND PRECAUTIONS

5.4 Cardiac Disorders

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the relapsed multiple myeloma study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the VELCADE and dexamethasone groups, 5% and 4%, respectively. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

6 ADVERSE REACTIONS

6.1 Clinical Trials Safety Experience

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study: Four deaths were considered to be VELCADE related in this relapsed multiple myeloma study: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four deaths were considered dexamethasone-related: 2 cases of sepsis, 1 case of bacterial meningitis, and 1 case of sudden death at home.

***Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Integrated Summary of Safety*:** In total, 2% of the patients died and the cause of death was considered by the investigator to be possibly related to study drug: including reports of cardiac arrest, congestive heart failure, respiratory failure, renal failure, pneumonia and sepsis.

Additional Adverse Events from Clinical Studies

Cardiac disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, Torsades de pointes, ventricular tachycardia

6.2 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide post-marketing experience with VELCADE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: atrioventricular block complete, cardiac tamponade

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology

Cardiovascular Toxicity: Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses $\geq$1.2 mg/m^2 induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

APPENDIX B. MEDDRA PREFERRED TERMS IN THE TORSADES DE POINTES/QT PROLONGATION – NARROW STANDARDIZED MEDDRA QUERY

Electrocardiogram QT interval abnormal

Electrocardiogram QT prolonged

Long QT syndrome

Torsade de pointes

Cardiac arrest

Cardiac death

Cardiac fibrillation

Cardio-respiratory arrest

Sudden cardiac death

Ventricular arrhythmia

Ventricular fibrillation

Ventricular flutter

Ventricular tachycardia

APPENDIX C. AERS CASE NUMBERS AND MANUFACTURER CONTROL NUMBERS

Case Numbers	Manufacturer Control Numbers
4009954	S03-341-539
4028819	S03-341-638
4108943	CH-GLAXOSMITHKLINE-B0325768A
4112405	2004PK00428
4124373	M04-341-088
4125168	M04-341-087
4158743	M04-341-099
4160468	M04-341-060
4173246	2004-00133
5657343	2004-00614
5660233	2004-00619
5662373	2004-00533
5706602	2004-00389
5735618	163-20785-04090565
5759448	CTU 242114 E
5796306	163-20785-05040553
5812177	2005-01069
5812180	2005-01088
5823501	2004-00769
5835284	CTU 252483E
5867617	2005-00721
5881860	2005-01460
5883290	2005-00342
5927749	2005-02237
5931359	2005-02192
5937948	2005-02331
5941677	S03-341-002
5955126	2005-02487
5955265	2005-02544
5962350	2005-02678
5968299	GB-JNJFOC-20060102958
5972420	2006-00102
5991975	2006-00151
6019003	2006-00513
6027736	2006-00413
6033137	2006-00481
6048818	US-GLAXOSMITHKLINE-A0605718A
6050522	CTU 276542
6054290	2006-00193
6056044	2006-01168
6084562	2004-00841
6093427	2005-01933
6118153	2006-00423
6121240	2006-02076
6135129	2006-02278
6135139	2006-02277
6174125	I03-341-049

6189314	2006-02975
6189792	2006-03017
6209832	2006-03120
6213069	163-21880-06110029
6214067	2006-03250
6214717	2006-03206
6216751	234160
6237245	2007-00060
6256343	2007-00324
6277199	2007-00723
6291113	2007-00852
6319999	2007-01247
6337374	2007-01634
6347783	2007-01882
6359439	2007-02249
6447578	2007-03391
6455747	2007-03433
6469320	2007-03659
6469678	US-AVENTIS-200720407GDDC
6475641	2007-03748
6480254	CTU 318393
6530219	2008-00018
6556920	2008-00338
6565693	2008-00853
6567860	2008-00423
6571949	2008-00470
6580044	IT-JNJFOC-20080302726
6597119	WAES 0707USA03463
6605919	IT-JNJFOC-20080401067
6636256	2008-01301
6636304	2008-00670
6637946	163-21880-07110046
6638067	2008-01366
6652655	2008-01561
6682667	2008-01272
6690864	2008-01939
6694892	2008-02258
6699282	2007-02203
6704741	2008-02416
6720288	2008-02686
6778958	2008-03371
6782221	2008-03513
6782844	2008-03470
6809607	2008-04027
6829493	2008-04173
6835755	2008-04365
6841467	2008-04331
6865897	2008-04588
6874027	163-20785-07011115
6877960	2008-04758
6899029	CTU 363688

6915932	2009SP002820
6919775	2009-00430
6931272	A0771924A
6931279	A0772123B
6932370	A0772145A
6941263	2009-00463
6943109	2009-00264
6951676	PT-CELGENEUS-130-20785-09031384
6961229	2009-01045
6976415	CTU 373782
6979514	CTU 374131
6980246	2009-01434
6998849	2009-01741
7014393	2009-02063
7015514	2009-02093
7026151	US-JNJFOC-20090604821
7040700	2009-02359
7066052	CTU 385984
7104983	2009-03341
7104985	2009-03339
7108019	2009-03388
7109434	CTU 391052
7133409	2009-03200
7133876	US-CUBIST-2009S1000404
7141526	2009-03695
7143226	2009-03831
7155971	2009-03916
7156047	2009-03710
7173219	2009-04348
7191640	US-MILLENNIUM PHARMACEUTICALS, INC.-2009-04868
7209679	US-JNJFOC-20091200598
7223895	WAES 0909USA04476
7238992	207-02249
7252250	IT-MPIJNJ-2010-00830
7269732	IT-MILLENNIUM PHARMACEUTICALS, INC.-2010-00973
7272849	US-MPIJNJ-2010-01034
7354845	A0854356A
7362463	US-MPIJNJ-2010-01775
7362475	US-MPIJNJ-2010-02141
7367180	GB-MPIJNJ-2010-02074
7394498	JP-MPIJNJ-2010-02628
7402001	US-MPIJNJ-2010-02698
7414840	WAES 1005USA02826
7498463	WAES 1006USA03726
7511547	US-JNJFOC-20100705444
7511696	US-JNJFOC-20100705492
7544634	US-GENENTECH-305317
7545620	US-CELGENEUS-163-21880-10070842
7566389	CH-CELGENEUS-151-20785-10081536
7569790	US-MILLENNIUM PHARMACEUTICALS, INC.-2010-04496
7610430	GR-MPIJNJ-2010-04970

7619089	US-CELGENEUS-163-21880-10100086
7621508	DE-MPIJNJ-2010-05000
7626369	GB-MPIJNJ-2010-05131
7634049	US-CELGENEUS-163-21880-10091108
7699957	US-CEPHALON-2010005958
7701242	FR-MILLENNIUM PHARMACEUTICALS, INC.-2010-06110
7704534	WAES 1010USA00064
7714526	US-MPIJNJ-2010-05748
7770987	WAES 1012USA03324
7814372	IT-CELGENEUS-083-20785-11021324
7831289	IT-JNJFOC-20110205711
7861413	US-MILLENNIUM PHARMACEUTICALS, INC.-2011-00916
7875902	A0920141A

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/s/

KATHERINE M COYLE
07/05/2011

ROBERT G PRATT
07/05/2011

BINDI M NIKHAR
07/05/2011

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/s/

AMY C BAIRD
08/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021602/S-027

FILING COMMUNICATION

Millennium Pharmaceuticals, Inc.
Attention: Eileen Bedell
Director, Regulatory Affairs
40 Landsdowne Street
Cambridge, MA 02139

Dear Ms. Bedell:

Please refer to your Supplemental New Drug Application (sNDA) dated March 23, 2011, received March 23, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VELCADE® (bortezomib) for Injection.

We also refer to your submission dated April 7, 2011.

This supplemental application proposes the following change(s): to support the subcutaneous route of administration as an alternative to the currently approved intravenous route of administration.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is January 23, 2012.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 19, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Division Director
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
05/27/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, April 04, 2011 11:31 AM
To: 'Irache.Visiers@MPI.com'
Subject: NDA 021602/S-027 Velcade - FDA Clinical Request for Information

Please refer to your supplemental NDA application for NDA 021602/S-027 Velcade dated March 23, 2011, which provides for subcutaneous route of administration (ROA) as an alternative to the existing intravenous ROA.

Per the request of the FDA Clinical review team, please provide the following information:

1. Analysis of ORR by site.
2. Analysis of ORR by investigator.
3. Justification of the applicability of the results of this study conducted in a non-US population to a US population.

Please attempt to provide a response NLT April 6, 2011, via email to amy.baird@fda.hhs.gov. Also, provide the response as an official submission to NDA 021602/S-027.

Please do not hesitate to contact me should you have any questions.

Regards,
Amy

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
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/s/

AMY C BAIRD
04/04/2011