เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

VELCADE®

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name

VELCADE (bortezomib)

1.2 Strength

Each vial contains bortezomib 1.0 mg/ml

1.3 Pharmaceutical Dosage Form

Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

VELCADE (bortezomib) for Injection is an antineoplastic agent available for intravenous injection (IV) or subcutaneous (SC) use.

2.2 Quantitative Declaration

Each single use vial contains:

- 1.0 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 10 mg mannitol, USP/EP (IV use only), or
- 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP/EP (IV or SC use).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VELCADE (bortezomib) for Injection is supplied as individually cartoned 5 mL vials containing 1 mg of bortezomib or 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

- 1.0 mg single use vial
- 3.5 mg single use vial

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

VELCADE (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma.

4.2 Posology and Method of Administration

VELCADE may be administered:

- Intravenously (at a concentration of 1 mg/mL) as a 3 to 5 second bolus injection or
- Subcutaneously (at a concentration of 2.5 mg/mL)

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

At least 72 hours should elapse between consecutive doses of VELCADE.

VELCADE IS FOR INTRAVENOUS OR SUBCUTANEOUS USE ONLY. Intrathecal administration has resulted in death.

VELCADE retreatment may be considered for multiple myeloma patients who had previously responded to treatment with VELCADE (*see below and Pharmacodynamic Properties, 5.1)*.

Posology

Monotherapy

Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Recommended Dosage

The recommended dose of VELCADE is 1.3 mg/m^2/dose 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, for relapsed multiple myeloma, 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). At least 72 hours should elapse between consecutive doses of VELCADE.

Dose Modification and Reinitiation of Therapy

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 Special Warnings and Special Precautions for Use, 4.4*). 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 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

Neuropathic Pain and/or Peripheral Sensory Neuropathy

The following table contains the recommended dose modification for the management of patients who experience VELCADE-related neuropathic pain and/or peripheral sensory neuropathy (Table 1). Severe autonomic neuropathy resulting in treatment interruption or discontinuation has been reported. Patients with pre-existing severe neuropathy should be treated with VELCADE only after careful risk/benefit assessment.

Table 1: Recommended Dose Modification for VELCADE-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	**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))[b]	Reduce VELCADE to 1.0 mg/m^2 OR Change VELCADE treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[c])	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

[a] Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

[b] *Instrumental ADL*: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.

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

Combination Therapy

Previously Untreated Multiple Myeloma - Patients who are Not Eligible for Stem Cell Transplantation

Recommended Dosage in Combination with Melphalan and Prednisone

VELCADE (bortezomib) for Injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 2. 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).

Table 2: Recommended Dosage Regimen for VELCADE when used in combination with melphalan and prednisone for Patients with Previously Untreated Multiple Myeloma who are not eligible for stem cell transplantation

Twice Weekly VELCADE (Cycles 1-4)

Week	**1**				**2**		**3**	**4**		**5**		**6**
Vc (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
m(9 mg/m^2) p(60 mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Once Weekly VELCADE (Cycles 5-9)

Week	**1**				**2**	**3**	**4**	**5**	**6**
Vc (1.3 mg/m$^{2)}$	Day 1	--	--	--	Day 8	rest period	Day 22	Day 29	rest period
m (9 mg/m^2) p (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	rest period	--	--	rest period

Vc = VELCADE; m = melphalan, p=prednisone

Dose Management Guidelines for Combination Therapy with Melphalan and Prednisone

Dose modification and reinitiation of therapy when VELCADE is administered in combination with melphalan and prednisone**.**

Prior to initiating a new cycle of therapy:

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

Table 3: Dose Modifications During Subsequent Cycles

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 $\leq 30 \times 10^9$/L or ANC $\leq$ 0.75 x 10^9/L on a VELCADE dosing day (other than day 1)	VELCADE dose should be withheld
• If several VELCADE doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	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 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 and/or modify VELCADE as outlined in Table 1.

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

Previously Untreated Multiple Myeloma – Patients who are Eligible for Stem Cell Transplantation

Recommended Dosage

The recommended starting dose of VELCADE in combination with other medicinal products used for the treatment of multiple myeloma is 1.3 mg/m^2 to be administered twice weekly on Days 1, 4, 8, and 11, followed by a rest period of 10-18 days, which is considered a treatment cycle. Three to 6 cycles should be administered. At least 72 hours should elapse between consecutive doses of VELCADE.

For VELCADE dosage adjustments for transplant eligible patients follow dose modification guidelines described under monotherapy (Table 1) above.

For dosing instructions for other medicinal products combined with VELCADE, see manufacturer's prescribing information.

Relapsed Multiple Myeloma

Recommended Dosage in Combination with Pegylated Liposomal Doxorubicin

For VELCADE dosage and dose modifications, see Monotherapy.

Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the VELCADE 3 week regimen as a 1 hour intravenous infusion administered after the VELCADE injection.

For additional information concerning pegylated liposomal doxorubicin, see manufacturer's prescribing information.

Recommended Dosage in Combination with Dexamethasone

For VELCADE dosage and dose modifications, see Monotherapy.

Dexamethasone is administered orally at 20 mg on the day of, and the day after, VELCADE administration.

For additional information concerning dexamethasone, see manufacturer's prescribing information.

Retreatment for Multiple Myeloma

Patients who have previously responded to treatment with VELCADE (either alone or in combination) and who have relapsed should be started on retreatment at the last tolerated dose. Refer to Monotherapy for dosing schedule.

Previously Untreated Mantle Cell Lymphoma

Recommended Dosage in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

For VELCADE dosage, see Monotherapy. Six VELCADE cycles are administered. For patients with a response first documented at Cycle 6, two additional VELCADE cycles are recommended.

The following medicinal products are administered on Day 1 of each VELCADE 3 week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2, and doxorubicin at 50 mg/m^2. Prednisone is administered orally at 100 mg/m^2 on Days 1, 2, 3, 4 and 5 of each treatment cycle.

Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Prior to the first day of each cycle (other than Cycle 1):

- Platelet count should be ≥ 100 x 10^9/L and absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L
- Hemoglobin should be ≥ 8 g/dL (≥ 4.96 mmol/L)
- Non-hematologic toxicity should have recovered to Grade 1 or baseline

VELCADE treatment must be withheld at the onset of any Grade 3 non-hematological or Grade 3 hematological toxicities, excluding neuropathy *(see Special Warnings and Special Precautions for Use,4.4)*. For dose adjustments, see Table 4 below.

Table 4: Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Toxicity	**Posology modification or delay**
Hematological toxicity • ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10 × 10^9/L	VELCADE therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 0.75 × 10^9/L and a platelet count ≥ 25 × 10^9/L. • If, after VELCADE has been held, the toxicity does not resolve, as defined above, then VELCADE must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 0.75 × 10^9/L and a platelet count ≥ 25 × 10^9/L, 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).
• If platelet counts < 25 × 10^9/L or ANC < 0.75 × 10^9/L on a VELCADE dosing day (other than Day 1)	VELCADE dose should be withheld

Toxicity	Posology modification or delay
Grade ≥ 3 non-hematological toxicities	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. 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 and/or modify VELCADE as outlined in Table 1.

For dosing instructions for rituximab, cyclophosphamide, doxorubicin, or prednisone, see manufacturer's prescribing information.

Special Patient Populations

Elderly Patients
See local product information.

Pediatric Patients
See local product information.

Impaired Renal Function

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, the drug should be administered after the dialysis procedure *(see Pharmacokinetic Properties, 5.2)*.

Impaired Hepatic Function

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELCADE dose. For patients with moderate or severe hepatic impairment, see Table 5 below**,** *(also, see Pharmacokinetic Properties, 5.2)*.

Table 5: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose in Multiple Myeloma and Relapsed Mantle Cell Lymphoma (1.3 mg/m^2 twice weekly)
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x–1.5x ULN	Any	None
Moderate	> 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	> 3x ULN	Any	

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

Method of Administration

VELCADE is administered intravenously or subcutaneously. When administered intravenously, VELCADE is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection. For subcutaneous administration, the reconstituted solution is injected into the thighs (right or left) or abdomen (right or left). Injection sites should be rotated for successive injections.

If local injection site reactions occur following VELCADE injection subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously, or changed to IV injection.

4.3 Contraindications

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

4.4 Special Warnings and Special Precautions for Use

VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

There have been fatal cases of inadvertent intrathecal administration of VELCADE. VELCADE is for IV and subcutaneous use only**. DO NOT ADMINISTER VELCADE INTRATHECALLY.**

Overall, the safety profile of patients treated with VELCADE in monotherapy was similar to that observed in patients treated with VELCADE in combination with melphalan and prednisone.

Peripheral Neuropathy

VELCADE treatment causes a peripheral neuropathy (PN) that is predominantly sensory. However, cases of severe motor neuropathy with or without sensory 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 study comparing VELCADE IV vs SC the incidence of Grade ≥2 peripheral neuropathy events was 24% for SC and 41% for IV (p=0.0124). Grade ≥3 peripheral neuropathy occurred in 6% of subjects in the SC treatment group, compared with 16% in the IV treatment group (p=0.0264) (Table 9). Therefore, patients with pre-existing PN or at high risk of peripheral neuropathy may benefit from starting VELCADE subcutaneously.

Patients experiencing new or worsening peripheral neuropathy may require a change in dose, schedule or route of administration to SC *(see Posology and Method of Administration, 4.2)*. Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the single agent phase 3 multiple myeloma study of VELCADE vs dexamethasone. 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.

The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension

In phase 2 and 3 single agent multiple myeloma studies, the incidence of hypotension (postural, orthostatic, and Hypotension Not Otherwise Specified) was 11% to 12%. 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, or administration of mineralocorticoids and/or sympathomimetics *(see Undesirable Effects, 4.8)*.

Cardiac Disorders

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported, including reports in patients with few or no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the single agent phase 3 multiple myeloma study of VELCADE vs dexamethasone, the incidence of any treatment-emergent cardiac disorder was 15% and 13% 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.

Hepatic Events

Rare 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.

Pulmonary Disorders

There have been rare 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. A higher proportion of these events have been reported in Japan. In the event of new or worsening

pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients treated appropriately.

In a clinical trial, 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.

Laboratory Tests

Complete blood counts (CBC) should be frequently monitored throughout treatment with VELCADE.

Thrombocytopenia/Neutropenia

VELCADE is associated with thrombocytopenia and neutropenia *(see Undesirable Effects, 4.8)*. Platelets were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet count decrease and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied.

Platelet counts should be monitored prior to each dose of VELCADE. VELCADE therapy should be held when the platelet count is <25,000/uL *(see Posology and Method of Administration, 4.2 and Undesirable Effects, 4.8)*. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE. Transfusion and supportive care may be considered.

In the single-agent multiple myeloma study of VELCADE vs dexamethasone, 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. The incidence of significant bleeding events (≥ Grade 3) was similar on both the VELCADE (4%) and dexamethasone (5%) arms.

Table 6: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Single Agent Phase 3 Multiple Myeloma Study of VELCADE vs Dexamethasone

Pretreatment Platelet Count[a]	Number of Patients (N=331)[b]	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] A baseline platelet count of 50,000/μL was required for study eligibility.

[b] Data were missing at baseline for 1 patient.

In the combination study of VELCADE with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia adverse events (≥ Grade 4) was 32% versus 2% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm. The incidence of bleeding adverse events (≥ Grade 3) was 1.7% (4 patients) in the VcR-CAP arm and was 1.2% (3 patients) in the R-CHOP arm.

There were no deaths due to bleeding events in either arm. There were no CNS bleeding events in the VcR-CAP arm; there was 1 bleeding event in the R-CHOP arm. Platelet transfusions were given to 23% of the patients in the VcR-CAP arm and 3% of the patients in the R-CHOP arm.

The incidence of neutropenia (≥ Grade 4) was 70% in the VcR-CAP arm and was 52% in the R-CHOP arm. The incidence of febrile neutropenia (≥ Grade 4) was 5% in the VcR-CAP arm and

was 6% in the R-CHOP arm. Colony-stimulating factor support was provided at a rate of 78% in the VcR-CAP arm and 61% in the R-CHOP arm.

Gastrointestinal Adverse Events

VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting *(see Undesirable Effects, 4.8)* sometimes requiring use of antiemetics and antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration. Since patients receiving VELCADE therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

Tumor Lysis Syndrome

Because VELCADE is a cytotoxic agent and can rapidly kill malignant cells the complications of tumor lysis syndrome may occur. The 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.

Patients with 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 Posology and Method of Administration, 4.2 and Pharmacokinetic Properties, 5.2).*

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of PRES in patients receiving VELCADE. PRES 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 PRES, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known.

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

In vitro and animal *ex vivo* studies indicate that bortezomib is a weak inhibitor of cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metabolizer phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of VELCADE, showed a bortezomib AUC mean increase of 35%, based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent inhibitor of CYP2C19, on the pharmacokinetics of VELCADE there was no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients.

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of VELCADE showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. The concomitant use of VELCADE with strong CYP3A4 inducers is therefore not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort. In the same drug-drug interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.

A drug-drug interaction study assessing the effect of melphalan-prednisone on VELCADE showed a 17% increase in mean bortezomib AUC based on data from 21 patients. This is not considered clinically relevant.

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.

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

Drug Laboratory Test Interactions

None known.

4.6 Pregnancy and Lactation

Pregnancy

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE.

No placental transfer studies have been conducted with bortezomib. 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.

Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with VELCADE.

See Preclinical Safety Data, 5.3, for more information.

Lactation

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, women should be advised against breast feeding while being treated with VELCADE.

Fertility

Nonclinical 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.

4.7 Effects on Ability to Drive and Use Machines

VELCADE may cause tiredness, dizziness, fainting, or blurred vision. Patients should be advised not to drive or operate machinery if they experience these symptoms.

4.8 Undesirable Effects

Clinical Trials

Summary of Clinical Trials of VELCADE IV in Patients with Relapsed/Refractory Multiple Myeloma

The safety and efficacy of VELCADE were evaluated in 3 studies at the recommended dose of 1.3 mg/m^2. These included a phase 3 randomized, comparative study, versus dexamethasone of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy (M34101-039); a phase 2 single arm, open-label, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy (M34100-025); and a phase 2 dose-response clinical study in relapsed multiple myeloma for patients who had progressed or relapsed on or after first line therapy with VELCADE 1.0 mg/m^2 or 1.3 mg/m^2 (M34100-024).

Table 7: VELCADE Adverse Drug Reactions in Phase 2 and Phase 3 Relapsed/Refractory Multiple Myeloma Studies

	Study No.	
MedDRA System Organ Class Preferred Term	M34101-039 (N=331)	M34100-024/ M34100-025 (N=228[a])
Blood and lymphatic system disorders		
Thrombocytopenia	115 (35%)	97 (43%)
Anemia	87 (26%)	74 (32%)
Neutropenia	62 (19%)	55 (24%)
Leucopenia	24 (7%)	15 (7%)
Lymphopenia	15 (5%)	11 (5%)

	Study No.	
MedDRA System Organ Class Preferred Term	M34101-039 (N=331)	M34100-024/ M34100-025 (N=228[a])
Pancytopenia	2 (<1%)	6 (3%)
Febrile neutropenia	1 (<1%)	1 (<1%)
Cardiac disorders		
Arrhythmias	4 (1%)	2 (<1%)
Tachycardia	9 (3%)	17 (7%)
Atrial fibrillation	6 (2%)	2 (<1%)
Palpitations	5 (2%)	4 (2%)
Acute development or exacerbation of cardiac failure, including CHF	7 (2%)	8 (4%)
Pulmonary edema	6 (2%)	3 (1%)
Cardiogenic shock[b]	1 (<1%)	-
New onset of decreased left ventricular ejection fraction	1 (<1%)	-
Atrial flutter	1 (<1%)	-
Bradycardia	3 (<1%)	1 (<1%)
Ear & labyrinth disorders		
Hearing impairment	1 (<1%)	1 (<1%)
Eye disorders		
Blurred vision	9 (3%)	25 (11%)
Conjunctival infection and irritation	14 (4%)	7 (3%)
Gastrointestinal (GI) disorders		

	Study No.	
MedDRA System Organ Class Preferred Term	M34101-039 (N=331)	M34100-024/ M34100-025 (N=228[a])
Constipation	140 (42%)	97 (43%)
Diarrhea	190 (57%)	116 (51%)
Nausea	190 (57%)	145 (64%)
Vomiting	117 (35%)	82 (36%)
Gastrointestinal and abdominal pain, excluding oral and throat	80 (24%)	48 (21%)
Dyspepsia	32 (10%)	30 (13%)
Pharyngolaryngeal pain	25 (8%)	19 (8%)
Gastroesophageal reflux	10 (3%)	1 (<1%)
Eructation	2 (<1%)	4 (2%)
Abdominal distension	14 (4%)	13 (6%)
Stomatitis and mouth ulceration	24 (7%)	10 (4%)
Dysphagia	4 (1%)	5 (2%)
GI hemorrhage (upper and lower GI tract)[b]	7 (2%)	3 (1%)
Rectal hemorrhage (includes hemorrhagic diarrhea)	7 (2%)	3 (1%)
Tongue ulceration	2 (<1%)	1 (<1%)
Retching	3 (<1%)	2 (<1%)
Upper GI hemorrhage	1 (<1%)	-
Hematemesis	1 (<1%)	-
Oral mucosal petechiae	3 (<1%)	-

	Study No.	
MedDRA System Organ Class Preferred Term	M34101-039 (N=331)	M34100-024/ M34100-025 (N=228[a])
Ileus Paralytic	1 (<1%)	2 (<1%)
General disorders and administration site conditions		
Asthenic conditions	201 (61%)	149 (65%)
weakness	40 (12%)	44 (19%)
fatigue	140 (42%)	118 (52%)
lethargy	12 (4%)	9 (4%)
malaise	13 (4%)	22 (10%)
Pyrexia	116 (35%)	82 (36%)
Rigors	37 (11%)	27 (12%)
Edema of the lower limbs	35 (11%)	27 (12%)
Neuralgia	21 (6%)	5 (2%)
Chest Pain	26 (8%)	16 (7%)
Injection site pain and irritation	1 (<1%)	1 (<1%)
Injection site phlebitis	1 (<1%)	1 (<1%)
Hepatobiliary disorders		
Hyperbilirubinemia	1 (<1%)	-
Abnormal liver function tests	3 (<1%)	2 (<1%)
Hepatitis	2 (<1%) in study M34101-040[c]	-
Immune system disorders		

	Study No.	
MedDRA System Organ Class Preferred Term	M34101-039 (N=331)	M34100-024/ M34100-025 (N=228[a])
Drug hypersensitivity	1 (<1%)	1 (<1%)
Infections and infestations		
Upper respiratory tract infection	26 (8%)	41 (18%)
Nasopharyngitis	45 (14%)	17 (7%)
Lower respiratory tract and lung infections	48 (15%)	29 (13%)
Pneumonia[b]	21 (6%)	23 (10%)
Herpes zoster(including multidermatomal or disseminated)	42 (13%)	26 (11%)
Herpes simplex	25 (8%)	13 (6%)
Bronchitis	26 (8%)	6 (3%)
Postherpetic neuralgia	4 (1%)	1 (<1%)
Sinusitis	14 (4%)	15 (7%)
Pharyngitis	6 (2%)	2 (<1%)
Oral candidiasis	6 (2%)	3 (1%)
Urinary tract infection	13 (4%)	14 (6%)
Catheter related infection	10 (3%)	6 (3%)
Sepsis and bacteremia[b]	9 (3%)	9 (4%)
Gastroenteritis	7 (2%)	-
Injury, poisoning, and procedural complications		
Catheter related complication	7 (2%)	8 (4%)

	Study No.	
MedDRA System Organ Class Preferred Term	M34101-039 (N=331)	M34100-024/ M34100-025 (N=228[a])
Investigations		
Increased ALT	3 (<1%)	10 (4%)
Increased AST	5 (2%)	12 (5%)
Increased alkaline phosphatase	6 (2%)	8 (4%)
Increased GGT	1 (<1%)	4 (2%)
Metabolism and nutritional disorders		
Decreased appetite and anorexia	112 (34%)	99 (43%)
Dehydration	24 (7%)	42 (18%)
Hyperglycemia	5 (2%)	16 (7%)
Hypoglycemia	7 (2%)	4 (2%)
Hyponatremia	8 (2%)	18 (8%)
Tumor lysis syndrome	2 (<1%) in study M34101-040[c]	-
Musculoskeletal and connective tissue disorders		
Pain in limb	50 (15%)	59 (26%)
Myalgia	39 (12%)	32 (14%)
Arthralgia	45 (14%)	60 (26%)
Nervous system disorders		
Peripheral neuropathy[d]	120 (36%)	84 (37%)
Paresthesia and dysesthesia	91 (27%)	53 (23%)

	Study No.	
MedDRA System Organ Class Preferred Term	M34101-039 (N=331)	M34100-024/ M34100-025 (N=228[a])
Dizziness, excluding vertigo	45 (14%)	48 (21%)
Headache	85 (26%)	63 (28%)
Dysgeusia	17 (5%)	29 (13%)
Polyneuropathy	9 (3%)	1 (<1%)
Syncope	8 (2%)	17 (7%)
Convulsions	4 (1%)	-
Loss of consciousness	2 (<1%)	-
Ageusia	2 (<1%)	-
Psychiatric disorders		
Anxiety	31 (9%)	32 (14%)
Renal and urinary disorders		
Renal Impairment and Failure	21 (6%)	21 (9%)
Difficulty in micturition	2 (1%)	3 (1%)
Hematuria	5 (2%)	4 (2%)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	21 (6%)	23 (10%)
Cough	70 (21%)	39 (17%)
Dyspnea	65 (20%)	50 (22%)
Exertional dyspnea	21 (6%)	18 (8%)
Pleural effusion	4 (1%)	9 (4%)

	Study No.	
MedDRA System Organ Class Preferred Term	M34101-039 (N=331)	M34100-024/ M34100-025 (N=228[a])
Rhinorrhea	4 (1%)	14 (6%)
Hemoptysis	3 (<1%)	2 (<1%)
Skin and subcutaneous tissue disorders		
Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vasculitis	61 (18%)	47 (21%)
Urticaria	7 (2%)	5 (2%)
Vascular disorders		
Hypotension	20 (6%)	27 (12%)
Orthostatic/postural hypotension	14 (4%)	8 (4%)
Petechiae	6 (2%)	7 (3%)
Cerebral hemorrhage[b]	1 (<1%)	-

[a] All 228 patients received VELCADE at a dose of 1.3 mg/m^2

[b] includes fatal outcome

[c] A study of VELCADE at the recommended dose of 1.3 mg/m^2 in multiple myeloma patients who experienced progressive disease after receiving at least four previous therapies or after receiving high-dose dexamethasone in Protocol M34101-039

[d] including all preferred terms under the MedDRA HLT "peripheral neuropathy NEC"

Summary of Clinical Trials of VELCADE IV vs SC in Patients with Relapsed Multiple Myeloma

The safety and efficacy of VELCADE SC 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 IV vs SC in 222 patients with relapsed multiple myeloma.

Table 8: Incidence of VELCADE Adverse Drug Reactions reported in ≥ 10% of patients in the Phase 3 Relapsed Multiple Myeloma Study comparing VELCADE IV and SC

	IV			SC		
	(N=74)			(N=147)		
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						
Anemia	26 (35)	6 (8)	0	53 (36)	14 (10)	4 (3)
Leukopenia	16 (22)	4 (5)	1 (1)	29 (20)	9 (6)	0
Neutropenia	20 (27)	10 (14)	3 (4)	42 (29)	22 (15)	4 (3)
Thrombocytopenia	27 (36)	8 (11)	6 (8)	52 (35)	12 (8)	7 (5)
Gastrointestinal disorders						
Abdominal pain	8 (11)	0	0	5 (3)	1 (1)	0
Abdominal pain upper	8 (11)	0	0	3 (2)	0	0
Constipation	11 (15)	1 (1)	0	21 (14)	1 (1)	0
Diarrhea	27 (36)	3 (4)	1 (1)	35 (24)	2 (1)	1 (1)
Nausea	14 (19)	0	0	27 (18)	0	0
Vomiting	12 (16)	0	1 (1)	17 (12)	3 (2)	0
General disorders and administration site conditions						
Asthenia	14 (19)	4 (5)	0	23 (16)	3 (2)	0
Fatigue	15 (20)	3 (4)	0	17 (12)	3 (2)	0
Pyrexia	12 (16)	0	0	28 (19)	0	0
Infections and infestations						
Herpes zoster	7 (9)	1 (1)	0	16 (11)	2 (1)	0
Metabolism and nutrition disorders						

	IV (N=74)			SC (N=147)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥ 4	n (%)	3	≥ 4
Decreased appetite	7 (9)	0	0	14 (10)	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	8 (11)	2 (3)	0	8 (5)	1 (1)	0
Nervous system disorders						
Headache	8 (11)	0	0	5 (3)	0	0
Neuralgia	17 (23)	7 (9)	0	35 (24)	5 (3)	0
Peripheral sensory neuropathy	36 (49)	10 (14)	1 (1)	51 (35)	7 (5)	0
Psychiatric disorders						
Insomnia	8 (11)	0	0	18 (12)	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	9 (12)	2 (3)	0	11 (7)	2 (1)	0

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.

Percentages of toxicity grade sub-groups calculated with the number of subjects in each group as denominator.

Although, in general safety data were similar for the IV and SC treatment groups, the following table highlights differences larger than 10% in the overall incidence of adverse drug reactions between the two treatment arms.

Table 9: Incidence of Adverse Drug Reactions with >10% Difference in Overall Incidence between Treatment Arms in the Phase 3 Relapsed Multiple Myeloma Study comparing VELCADE IV and SC, by Toxicity Grade and Discontinuation

	---------- IV ---------- (N=74)			---------- SC ---------- (N=147)		
MedDRA System Organ Class	------- Category, n (%) -------			------- Category, n (%) -------		
MedDRA High Level Term	TEAE	G ≥ 3	Disc	TEAE	G ≥ 3	Disc
All subjects with TEAE	73 (99)	52 (70)	20 (27)	140 (95)	84 (57)	33 (22)
Gastrointestinal disorders						
Diarrhea (excl infective)	27 (36)	4 (5)	1 (1)	35 (24)	3 (2)	1 (1)
Gastrointestinal and abdominal pains (excl oral and throat)	14 (19)	0	0	9 (6)	1 (1)	0
General disorders and administration site conditions						
Asthenic conditions	29 (39)	7 (9)	1 (1)	40 (27)	6 (4)	2 (1)
Infections and infestations						
Upper respiratory tract infections	19 (26)	2 (3)	0	20 (14)	0	0
Nervous system disorders						
Peripheral neuropathies [a]	39 (53)	12 (16)	10 (14)	56 (38)	9 (6)	9 (6)

[a] Represents the high level term

TEAE = Treatment-Emergent Adverse Event; G ≥ 3 = Toxicity Grade greater than or equal to 3

Disc = Discontinuation of any study drug

Patients who received VELCADE subcutaneously compared to intravenous administration had 13% lower overall incidence of treatment-emergent adverse drug reactions that were grade 3 or higher in toxicity (57% vs 70% respectively), and a 5% lower incidence of discontinuation of VELCADE (22% vs 27%). The overall incidence of diarrhea (24% for the SC arm vs 36% for the IV arm), gastrointestinal and abdominal pain (6% for the SC arm vs 19% for the IV arm), asthenic conditions (27% for SC arm vs 39% for IV arm), upper respiratory tract infections (14% SC arm vs 26% IV arm) and peripheral neuropathy NEC (38% SC arm vs 53% IV arm) were 12%-15% lower in the subcutaneous group than the intravenous group. In addition, the incidence of peripheral neuropathies that were grade 3 or higher in toxicity was 10 % lower (6% for SC vs 16% for IV), and the discontinuation rate due to peripheral neuropathies was 8% lower for the subcutaneous group (5%) as compared to the intravenous group (12%).

Six percent of patients were reported to have had an adverse local reaction to SC administration, mostly redness. Only 2 (1%) subjects were reported as having severe reactions. These severe local reactions were 1 case of pruritus and 1 case of redness. These reactions seldom led to dose modifications and all resolved in a median of 6 days.

VELCADE Retreatment in Relapsed Multiple Myeloma

The following table describes adverse drug reactions reported for at least 10% of patients with relapsed multiple myeloma who received retreatment with VELCADE IV (Study MMY-2036).

Table 10: Incidence of VELCADE Adverse Drug Reactions reported in ≥ 10% of patients (Study MMY-2036)

	Vc Retreatment (MMY-2036)		
		Toxicity Grade	
	Total	3	≥4
Analysis Set: Safety, N	130		
Total no. subjects with adverse drug reactions, n (%)	126 (97)		
MedDRA system organ class Preferred term			
Blood and lymphatic system disorders			
Thrombocytopenia	71 (55)	19 (15)	14 (11)
Anemia	48 (37)	5 (4)	1 (1)
Neutropenia	23 (18)	9 (7)	0
Leukopenia	20 (15)	5 (4)	0
Gastrointestinal disorders			
Diarrhea	45 (35)	9 (7)	0
Constipation	36 (28)	0	0
Nausea	14 (11)	0	0

	Vc Retreatment (MMY-2036)		
		Toxicity Grade	
	Total	3	≥4
General disorders and administration site conditions			
Pyrexia	31 (24)	2 (2)	0
Asthenia	29 (22)	6 (5)	0
Fatigue	21 (16)	0	0
Edema peripheral	15 (12)	0	0
Infections and infestations			
Respiratory tract infection	17 (13)	3 (2)	1 (1)
Bronchitis	13 (10)	1 (1)	0
Nervous system disorders			
Peripheral sensory neuropathy	22 (17)	4 (3)	0
Neuropathy peripheral	13 (10)	3 (2)	0
Respiratory, thoracic and mediastinal disorders			
Cough	15 (12)	1 (1)	0
Dyspnea	14 (11)	1 (1)	0

Key: Vc = VELCADE; AE = Adverse event; NCI = National Cancer Institute; CTCAE = Common Toxicity Criteria for Adverse Events
Note: Percentages are calculated with the number of subjects in each group as denominator.
Adverse events are reported using MedDRA version 14.1.
In Study MMY-2036, for AEs where only a severity grade is reported, the severity grade is remapped to an NCI CTCAE toxicity grade.
AEs with missing toxicity grade are assigned grade 3.

Summary of Clinical Trials of VELCADE Combination Therapy in Patients with Relapsed Multiple Myeloma

The following table describe adverse drug reactions reported for at least 10% of patients with relapsed multiple myeloma who received VELCADE in combination with dexamethasone (Study MMY-2045) or VELCADE in combination with pegylated liposomal doxorubicin (Study DOXIL-MMY-3001).

Table 11: Most Frequent (at Least 10 Percent in Any Treatment Group) Treatment-Emergent Adverse Drug Reactions by Toxicity Grade, System Organ Class and Preferred Term; Safety Analysis Set (Studies DOXIL-MMY-3001 and MMY-2045)

			Vc Combination Therapy			
	Vc Monotherapy		Vc + DOXIL		Vc + Dex	
	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)
Analysis Set: Safety	318		318		163	
Total no. subjects with adverse drug reactions	301 (95)		314 (99)		154 (94)	
MedDRA system organ class						
Preferred term						
Gastrointestinal disorders						
Diarrhea	124 (39)	16 (5)	145 (46)	23 (7)	51 (31)	7 (4)
Nausea	126 (40)	3 (1)	154 (48)	8 (3)	20 (12)	1 (1)
Constipation	98 (31)	2 (1)	99 (31)	3 (1)	50 (31)	9 (6)
Vomiting	69 (22)	3 (1)	101 (32)	13 (4)	11 (7)	2 (1)
Stomatitis	11 (3)	1 (< 1)	56 (18)	7 (2)	1 (1)	0
Abdominal pain	24 (8)	4 (1)	34 (11)	2 (1)	11 (7)	1 (1)
Nervous system disorders						
Peripheral neuropathy [a]	143 (45)	35 (11)	133 (42)	22 (7)	79 (48)	23 (14)

			Vc Combination Therapy			
	Vc Monotherapy		Vc + DOXIL		Vc + Dex	
	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)
Neuralgia	63 (20)	14 (4)	54 (17)	9 (3)	26 (16)	4 (2)
Headache	56 (18)	0	59 (19)	3 (1)	9 (6)	0
Paraesthesia	31 (10)	0	41 (13)	1 (< 1)	22 (13)	2 (1)
Dizziness	26 (8)	4 (1)	32 (10)	4 (1)	14 (9)	0
General disorders and administration site conditions						
Fatigue	88 (28)	8 (3)	115 (36)	22 (7)	37 (23)	2 (1)
Pyrexia	71 (22)	4 (1)	100 (31)	4 (1)	21 (13)	4 (2)
Asthenia	56 (18)	12 (4)	71 (22)	19 (6)	33 (20)	2 (1)
Edema peripheral	27 (8)	1 (< 1)	32 (10)	1 (< 1)	43 (26)	3 (2)
Blood and lymphatic system disorders						
Thrombocytopenia	89 (28)	53 (17)	106 (33)	76 (24)	61 (37)	28 (17)
Neutropenia	71 (22)	51 (16)	114 (36)	102 (32)	12 (7)	6 (4)
Anemia	68 (21)	30 (9)	80 (25)	29 (9)	35 (21)	16 (10)
Infections and infestations						
Herpes zoster	29 (9)	6 (2)	34 (11)	6 (2)	16 (10)	1 (1)
Bronchitis	21 (7)	3 (1)	31 (10)	1 (< 1)	18 (11)	1 (1)
Upper respiratory tract infection	33 (10)	3 (1)	33 (10)	2 (1)	15 (9)	3 (2)
Musculoskeletal and connective tissue disorders						

	Vc Monotherapy		Vc Combination Therapy			
			Vc + DOXIL		Vc + Dex	
	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)	Total n (%)	Grade ≥3 n (%)
Back pain	39 (12)	6 (2)	39 (12)	4 (1)	25 (15)	2 (1)
Pain in extremity	48 (15)	8 (3)	34 (11)	1 (< 1)	16 (10)	2 (1)
Arthralgia	27 (8)	5 (2)	34 (11)	1 (< 1)	14 (9)	1 (1)
Respiratory, thoracic and mediastinal disorders						
Cough	38 (12)	0	58 (18)	0	26 (16)	1 (1)
Dyspnea	28 (9)	10 (3)	34 (11)	3 (1)	13 (8)	3 (2)
Metabolism and nutritional disorders						
Decreased appetite	50 (16)	1 (< 1)	83 (26)	8 (3)	9 (6)	0
Skin and subcutaneous tissue disorders						
Rash	29 (9)	3 (1)	48 (15)	2 (1)	8 (5)	0
Investigations						
Weight decreased	12 (4)	0	37 (12)	0	3 (2)	0
Psychiatric disorders						
Insomnia	43 (14)	2 (1)	35 (11)	0	18 (11)	1 (1)

Key: Vc = VELCADE; Dex = dexamethasone; NCI = National Cancer Institute; CTCAE = Common Toxicity Criteria for Adverse Events
[a] Includes the preferred terms of neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and polyneuropathy.
Note: Percentages are calculated with the number of subjects in each group as denominator.
Adverse events are reported using MedDRA version 14.1.
In Study MMY-2045, for AEs where only a severity grade is reported, the severity grade is remapped to an NCI CTCAE toxicity grade.

Summary of Clinical Trials in Patients with Previously Untreated Multiple Myeloma

The following table describes safety data from 340 patients with previously untreated multiple myeloma who received VELCADE IV (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective phase 3 study.

Table 12: Treatment-Emergent Drug-Related Adverse Events reported in ≥ 10% of patients treated with VELCADE IV in combination with melphalan and prednisone

	Vc-MP (n=340)			MP (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	164 (48)	60 (18)	57 (17)	140 (42)	48 (14)	39 (12)
Neutropenia	160 (47)	101 (30)	33 (10)	143 (42)	77 (23)	42 (12)
Anemia	109 (32)	41 (12)	4 (1)	156 (46)	61 (18)	18 (5)
Leukopenia	108 (32)	64 (19)	8 (2)	93 (28)	53 (16)	11 (3)
Lymphopenia	78 (23)	46 (14)	17 (5)	51 (15)	26 (8)	7 (2)
Gastrointestinal Disorders						
Nausea	134 (39)	10 (3)	0	70 (21)	1 (<1)	0
Diarrhea	119 (35)	19 (6)	2 (1)	20 (6)	1 (<1)	0
Vomiting	87 (26)	13 (4)	0	41 (12)	2 (1)	0
Constipation	77 (23)	2 (1)	0	14 (4)	0	0
Abdominal Pain Upper	34 (10)	1 (<1)	0	20 (6)	0	0
Nervous System Disorders						
Peripheral Neuropathy	156 (46)	42 (12)	2 (1)	4 (1)	0	0
Neuralgia	117 (34)	27 (8)	2 (1)	1 (<1)	0	0
Paraesthesia	42 (12)	6 (2)	0	4 (1)	0	0

	Vc-MP (n=340)			MP (n=337)		
MedDRA System Organ Class	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Preferred Term	n (%)	3	≥4	n (%)	3	≥4
General Disorders and Administration Site Conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (<1)	1 (<1)
Infections and Infestations						
Herpes Zoster	39 (11)	11 (3)	0	9 (3)	4 (1)	0
Metabolism and Nutrition Disorders						
Anorexia	64 (19)	6 (2)	0	19 (6)	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	38 (11)	2 (1)	0	7 (2)	0	0
Psychiatric Disorders						
Insomnia	35 (10)	1 (<1)	0	21 (6)	0	0

Herpes Zoster Virus Reactivation

Physicians should consider using antiviral prophylaxis in patients being treated with Velcade. In the phase 3 study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with VcMP compared with MP (14% vs 4% respectively). Antiviral prophylaxis was administered to 26% of the patients in the VcMP arm. The incidence of herpes zoster among patients in the VcMP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Adverse Drug Reactions Noted in Patients with Previously Untreated Multiple Myeloma Eligible for Stem Cell Transplantation

The following table describes adverse drug reactions considered by the Company to have at least a possible causal relationship to VELCADE from patients with previously untreated multiple myeloma eligible for stem cell transplantation who received VELCADE IV (1.3 mg/m2). 410 patients were treated with VELCADE in combination with doxorubicin and dexamethasone compared with 411 patients treated with vincristine, doxorubicin and dexamethasone in Study MMY-3003, 239 were treated with VELCADE in combination with dexamethasone alone compared with 239 patients treated with vincristine, doxorubicin and dexamethasone in Study IFM 2005-01, and 130 were treated with VELCADE in combination with thalidomide and dexamethasone compared with 126 patients treated with thalidomide and dexamethasone in Study MMY-3010. For these 3 studies conducted in the transplant setting (MMY3003, IFM2005-01, MMY3010), only the adverse reactions during the induction phase of treatment are considered for the table.

Table 13: Incidence of Most Frequent (≥10% in Either Treatment Group) Treatment-Emergent Adverse Drug Reactions during Induction Stage

(VELCADE Transplant Integrated Analysis of Safety: Safety Analysis Set)

	---------- Vc-Based ----------			*---------- Non Vc-Based ----------*		
	(N=779)			*(N=776)*		
MedDRA System Organ Class	Total	- TOXICITY GRADE – n(%)		Total	- TOXICITY GRADE –n (%)	
Preferred Term	n (%)	2	≥ 3	n (%)	2	≥ 3
Total no. subjects with adverse drug reactions	715 (92)			679 (88)		
Gastrointestinal disorders						
Constipation	242 (31)	89 (11)	10 (1)	214 (28)	67 (9)	8 (1)
Nausea	215 (28)	71 (9)	22 (3)	206 (27)	77 (10)	9 (1)
Diarrhea	133 (17)	29 (4)	23 (3)	110 (14)	26 (3)	6 (1)
Vomiting	95 (12)	30 (4)	18 (2)	87 (11)	35 (5)	6 (1)
Nervous system disorders						
Neuropathy peripheral	147 (19)	53 (7)	20 (3)	54 (7)	11 (1)	4 (1)
Paraesthesia	101 (13)	24 (3)	11 (1)	80 (10)	15 (2)	2 (<1)
Peripheral sensory neuropathy	101 (13)	41 (5)	19 (2)	55 (7)	13 (2)	1 (<1)
Headache	64 (8)	23 (3)	4 (1)	76 (10)	23 (3)	1 (<1)
General disorders and administration site conditions						
Fatigue	158 (20)	50 (6)	21 (3)	161 (21)	68 (9)	21 (3)
Pyrexia	153 (20)	56 (7)	25 (3)	159 (20)	40 (5)	36 (5)

Asthenia	110 (14)	33 (4)	16 (2)	91 (12)	33 (4)	10 (1)
Blood and lymphatic system disorders						
Thrombocytopenia	239 (31)	54 (7)	63 (8)	171 (22)	27 (3)	27 (3)
Anemia	211 (27)	95 (12)	55 (7)	222 (29)	108 (14)	77 (10)
Leukopenia	196 (25)	51 (7)	109 (14)	206 (27)	53 (7)	120 (15)
Infections and infestations						
Herpes zoster	86 (11)	50 (6)	24 (3)	18 (2)	9 (1)	5 (1)
Metabolism and nutrition disorders						
Hyperglycemia	122 (16)	46 (6)	26 (3)	138 (18)	46 (6)	31 (4)
Hyponatremia	100 (13)	2 (<1)	29 (4)	82 (11)	6 (1)	12 (2)
Psychiatric disorders						
Insomnia	96 (12)	32 (4)	6 (1)	82 (11)	30 (4)	6 (1)

Vc=VELCADE

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

Incidence is based on the number of subjects experiencing at least 1 adverse reaction, not the number of events.

Adverse Events are coded using MedDRA 13.1.

Summary of the Clinical Trial in Patients with Relapsed Mantle Cell Lymphoma

Safety data for patients with relapsed mantle cell lymphoma were evaluated in a phase 2 study [M34103-053 (PINNACLE)], which included 155 patients treated with VELCADE at the recommended dose of 1.3 mg/m^2. The safety profile of VELCADE in these patients was similar

to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, anemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and pruritis were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.

Summary of Clinical Trial in Patients with Previously Untreated Mantle Cell Lymphoma

Table 14 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received VELCADE (1.3 mg/m^2) administered IV in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (VcR-CAP) in a prospective randomized study.

The incidences of Grade ≥ 3 bleeding events were similar between the 2 arms (4 patients in the VcR-CAP arm and 3 patients in the R-CHOP arm). All of the Grade ≥ 3 bleeding events resolved without sequelae in the VcR-CAP arm.

Infections were reported for 31% of patients in the VcR-CAP arm and 23% of the patients in the R-CHOP arm. Respiratory tract and lung infections were reported, with the predominant preferred term of pneumonia (VcR-CAP 8% versus R-CHOP 5%).

The incidence of herpes zoster reactivation was 4.6% in the VcR-CAP arm and 0.8% in the R-CHOP arm. Antiviral prophylaxis was mandated by protocol amendment.

Table 14: Most Commonly Reported Adverse Reactions (≥ 5%) with Grades 3 and ≥ 4 Intensity in the Mantle Cell Lymphoma Study of VcR-CAP versus R-CHOP (N=482) (Study LYM-3002)

	VcR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Blood and lymphatic system disorders						
Neutropenia	209 (87)	32 (13)	168 (70)	172 (71)	31 (13)	125 (52)
Leukopenia	116 (48)	34 (14)	69 (29)	87 (36)	39 (16)	27 (11)
Anemia	106 (44)	27 (11)	4 (2)	71 (29)	23 (10)	4 (2)

	VcR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Thrombocytopenia	172 (72)	59 (25)	76 (32)	42 (17)	9 (4)	3 (1)
Febrile neutropenia	41 (17)	24 (10)	12 (5)	33 (14)	17 (7)	15 (6)
Lymphopenia	68 (28)	25 (10)	36 (15)	28 (12)	15 (6)	2 (1)
Nervous system disorders						
Peripheral sensory neuropathy	53 (22)	11 (5)	1 (< 1)	45 (19)	6 (3)	0
Neuropathy peripheral	18 (8)	4 (2)	0	18 (7)	2 (1)	0
Hypoesthesia	14 (6)	3 (1)	0	13 (5)	0	0
Paraesthesia	14 (6)	2 (1)	0	11 (5)	0	0
Neuralgia	25 (10)	9 (4)	0	1 (< 1)	0	0
General disorders and administration site conditions						
Fatigue	43 (18)	11 (5)	1 (< 1)	38 (16)	5 (2)	0
Pyrexia	48 (20)	7 (3)	0	23 (10)	5 (2)	0
Asthenia	29 (12)	4 (2)	1 (< 1)	18 (7)	1 (< 1)	0
Edema peripheral	16 (7)	1 (< 1)	0	13 (5)	0	0
Gastrointestinal disorders						
Nausea	54 (23)	1 (< 1)	0	28 (12)	0	0

	VcR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Constipation	42 (18)	1 (< 1)	0	22 (9)	2 (1)	0
Stomatitis	20 (8)	2 (1)	0	19 (8)	0	1 (< 1)
Diarrhea	59 (25)	11 (5)	0	11 (5)	3 (1)	1 (< 1)
Vomiting	24 (10)	1 (< 1)	0	8 (3)	0	0
Abdominal distension	13 (5)	0	0	4 (2)	0	0
Infections and infestations						
Pneumonia	20 (8)	8 (3)	5 (2)	11 (5)	5 (2)	3 (1)
Skin and subcutaneous tissue disorders						
Alopecia	31 (13)	1 (< 1)	1 (< 1)	33 (14)	4 (2)	0
Metabolism and nutrition disorders						
Hyperglycemia	10 (4)	1 (< 1)	0	17 (7)	10 (4)	0
Decreased appetite	36 (15)	2 (1)	0	15 (6)	1 (< 1)	0
Hypokalemia	11 (5)	3 (1)	1 (< 1)	6 (2)	1 (< 1)	0
Vascular disorders						
Hypertension	15 (6)	1 (< 1)	0	3 (1)	0	0
Psychiatric disorders						

	VcR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Insomnia	16 (7)	1 (< 1)	0	8 (3)	0	0

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Postmarketing

Following is a list of ADRs which have been observed in postmarketing and are not included above:

Clinically significant adverse drug reactions are listed here if they have not been reported above.

The frequencies provided below reflect reporting rates of adverse drug reactions from the worldwide post-marketing experience with VELCADE. The frequencies provided below reflect reporting rates and precise estimates of incidence cannot be made. The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: very common (≥1/10), common (≥1/100 and < 1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and < 1/1,000), very rare (<1/10,000).

Table 15: Post-marketing Reports of Adverse Reactions

Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Thrombotic microangiopathy	Very Rare
Cardiac disorders	
Atrioventricular block complete, cardiac tamponade	Rare

Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye disorders	
Ophthalmic herpes, optic neuropathy, blindness	Rare
Chalazion/blepharitis	Rare
Gastrointestinal disorders	
Ischemic colitis, acute pancreatitis	Rare
Intestinal obstruction	Uncommon
Infections and infestations	
Herpes meningoencephalitis, septic shock	Rare
Progressive multifocal leukoencephalopathy[a]	Very rare
Immune system disorders	
Angioedema	Rare
Anaphylactic reaction	Very rare
Nervous system disorders	
Encephalopathy, autonomic neuropathy, posterior reversible encephalopathy syndrome	Rare
Guillain-Barré syndrome, demyelinating polyneuropathy	Very rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease *(see Special Warnings and Special Precautions for Use, 4.4)*, Pulmonary hypertension	Rare Rare
Skin and subcutaneous tissue disorders	

Stevens- Johnson Syndrome and toxic epidermal necrolysis Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Very rare Rare

[a] Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with VELCADE.

4.9 Overdose

Signs and Symptoms

Cardiovascular safety pharmacology studies in monkeys and dogs show that IV doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. The decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. In dog studies, a slight increase in the corrected QT interval was observed at a lethal dose.

Overdosage more than twice the recommended dose in patients has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

Management

There is no known specific antidote for VELCADE overdosage. In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature *(see Special Warnings and Special Precautions for Use, 4.4 and Posology and Method of Administration, 4.2).*

4.10 Drug Abuse and Dependence

Bortezomib has no known potential for abuse or dependence.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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.

Data from in vitro, *ex vivo*, and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

Clinical Studies

Phase 2 Clinical Studies in Relapsed Multiple Myeloma

The safety and efficacy of VELCADE IV were evaluated in an open-label, single-arm, multicenter study (M34100-25) of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Baseline patient and disease characteristics are summarized in Table 16.

An IV bolus injection of VELCADE 1.3 mg/m^2/dose was administered twice weekly for 2 weeks, followed by a 10-day rest period (21 day treatment cycle) for a maximum of 8 treatment cycles. The study employed dose modifications for toxicity *(see Posology and Method of Administration, 4.2)*. Patients who experienced a response to VELCADE treatment were allowed to continue VELCADE treatment in an extension study.

Table 16: Summary of Patient Population and Disease Characteristics[a]

	N = 202
Patient Characteristics	
Median age in years (range)	59 (34, 84)
Gender: Male/female	60% / 40%
Race: Caucasian/black/other	81% / 10% /8%
Karnofsky Performance Status score ≤70	20%
Hemoglobin <100 g/L	44%
Platelet count <75 x 10^9/L	21%
Disease Characteristics	
Type of myeloma (%): IgG/IgA/Light chain	60% / 24% / 14%
Median β_2-microglobulin (mg/L)	3.5

Median creatinine clearance (mL/min)	73.9
Abnormal cytogenetics	35%
Chromosome 13 deletion	15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any prior steroids, e.g., dexamethasone, VAD	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%
Any prior thalidomide therapy	83%
Received at least 2 of the above	98%
Received at least 3 of the above	92%
Received All 4 of the Above	66%
Any prior stem cell transplant/other high-dose therapy	64%
Prior experimental or other types of therapy	44%

[a] Based on number of patients with baseline data available

Responses to VELCADE alone are shown in Table 17. Response rates to VELCADE alone were determined by an independent review committee (IRC) based on criteria published by Bladé and others. Complete response required <5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-). Response rates using the SWOG criteria are also shown. SWOG response required a ≥75% reduction in serum myeloma protein and/or ≥90% urine protein. A total of 188 patients were evaluated for response; 9 patients with nonmeasurable disease could not be evaluated for response by the IRC. Five patients were excluded from the efficacy analyses because they had minimal prior therapy.

Ninety-eight percent of study patients received a starting dose of 1.3 mg/m^2 administered IV. Twenty-eight percent of these patients received a dose of 1.3 mg/m^2 throughout the study, while 33% of patients who started at a dose of 1.3 mg/m^2 had to have their dose reduced during the study. Sixty-three percent of patients had at least one dose held during the study. In general, patients who had a confirmed CR received 2 additional cycles of VELCADE treatment beyond confirmation. It was recommended that responding patients receive up to 8 cycles of VELCADE therapy. The mean number of cycles administered was 6.

The median time to response was 38 days (range 30 to 127 days).

The median survival of all patients enrolled was 16 months (range <1 to 18+ months).

Table 17: Summary of Disease Outcomes

Response Analyses (VELCADE monotherapy) N = 188	**N (%)**	**(95% CI)**
Overall Response Rate (Bladé) (CR + PR)	52 (27.7%)	(21, 35)
Complete Response (CR)[a]	5 (2.7%)	(1, 6)
Partial Response (PR)[b]	47 (25%)	(19, 32)
Clinical Remission (SWOG)[c]	33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	365 Days	(224, NE)

[a] Complete Response required < 5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-).

[b] Partial Response 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, stable bone disease and calcium.

[c] Clinical Remission (SWOG) required ≥75% reduction in serum myeloma protein and/or ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

In this study, the response rate to VELCADE was independent of the number and types of prior therapies. There was a decreased likelihood of response in patients with either >50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen in patients with chromosome 13 abnormalities.

A small dose-response study (M34100-24) was performed in 54 patients with multiple myeloma who received a 1.0 mg/m^2/dose or a 1.3 mg/m^2/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

Patients who did not obtain an optimal response to therapy with VELCADE alone (progressive or stable disease after 2 or 4 cycles, respectively) were able to receive high-dose dexamethasone in conjunction with VELCADE (i.e., 40 mg dexamethasone with each dose of VELCADE administered orally as 20 mg on the day of and 20 mg the day after VELCADE administration, (i.e., Days 1, 2, 4, 5, 8, 9, 11, and 12), thus 160 mg over 3 weeks). A total of 74 patients were

administered dexamethasone in combination with VELCADE and were assessed for response. Eighteen percent (13/74) of patients achieved or had an improved response (CR 11% or PR 7%) with combination treatment.

Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma comparing VELCADE to Dexamethasone

A prospective phase 3, international, randomized (1:1), stratified, open-label clinical trial [M34101-039 (APEX)] 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/µL. 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 18.

Table 18: Summary of Baseline Patient and Disease Characteristics in the Phase 3 APEX Trial

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

Patient Characteristics	VELCADE N=333	Dexamethasone N=336
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%
All Patients	(N=333)	(N=336)
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. Within each 3-week treatment cycle, VELCADE 1.3 mg/m^2/dose alone was administered by IV 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 IV 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 Posology and Method of Administration, 4.2)*.

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 to 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. At this time of study termination, a final statistical analysis was performed. Due to this early termination of the study, the median duration of follow-up for surviving patients (n=534) is limited to 8.3 months.

In the VELCADE arm, 34% of patients received at least 1 VELCADE dose in all 8 of the 3-week cycles of therapy, and 13% received at least 1 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 1 dose in all 4 of the 5-week treatment cycles of therapy, and 6% received at least 1 dose in all 9 cycles.

The time to event analyses and response rates from the phase 3 trial are presented in Table 19. 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 19: Summary of Efficacy Analyses in the Randomized Phase 3 APEX 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)
	6.2 mo	3.5 mo	7.0	5.6	4.9	2.9

Median [a] (95% CI)	(4.9, 6.9)	(2.9, 4.2)	(6.2, 8.8)	(3.4, 6.3)	(4.2, 6.3)	(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	
Median Response Duration						
CR[f]	9.9 mo	NE[i]	9.9 mo	NE	6.3 mo	NA[j]
nCR[f]	11.5 mo	9.2 mo	NE	NE	11.5 mo	9.2 mo
CR + PR[f]	8.0 mo	5.6 mo	8.1 mo	6.2 mo	7.8 mo	4.1 mo

[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.

[i] Not Estimable.

[j] Not Applicable, no patients in category.

Randomized, Open-Label Clinical Study in Relapsed Multiple Myeloma comparing VELCADE IV and SC

An open-label, randomized, phase 3 non-inferiority study (MMY-3021) compared the efficacy and safety of the subcutaneous administration (SC) of VELCADE versus the intravenous administration (IV). This study included 222 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 SC or IV 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 dexamethasone 20 mg daily on the day of and after VELCADE administration. Patients with baseline grade ≥ 2 peripheral neuropathy 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)

Baseline patient and disease characteristics are summarized in Table 20.

Table 20: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial of VELCADE IV vs SC (MMY-3021)

Patient Characteristics	**IV N=74**	**SC N=148**
Median age in years (range)	64.5 (38,86)	64.5 (42,88)
Gender: male/female	64% / 36%	50% / 50%
Race: caucasian/Asian	96% / 4%	97% / 3%
Karnofsky performance status score ≤70	16%	22%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	72% / 19% / 8%	65% / 26% / 8%
ISS staging[a] I/II/III (%)	27/41/32	27/41/32

Median β_2-microglobulin (mg/L)	4.25	4.20
Median albumin (g/L)	3.60	3.55
Creatinine clearance ≤30 mL/min [n (%)]	2 (3%)	5 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	2.93	2.68
Number of Prior Therapeutic Lines of Treatment		
1 prior line	65%	62%
> 1 prior line	35%	38%

[a] ISS Staging is derived from baseline central laboratory data.

This study met its primary objective of non-inferiority for response rate (CR + PR) after 4 cycles of single agent VELCADE for both the SC and IV routes, 42% in both groups. In addition, secondary response-related and time to event related efficacy endpoints showed consistent results for SC and IV administration (Table 21).

Table 21: Summary of efficacy analyses for the SC administration of VELCADE compared to IV (MMY-3021)

	IV VELCADE	**SC VELCADE**
Response-Evaluable Population[a]	**n=73**	**n=145**
Response Rate at 4 cycles		
ORR (CR+PR)	31 (42)	61 (42)
p-value[b]	0.00201	
CR n (%)	6(8)	9(6)
PR n (%)	25(34)	52(36)
nCR n (%)	4(5)	9(6)
Response Rate at 8 cycles		

ORR (CR+PR)	38(52)		76(52)
p-value[b]		0.0001	
CR n (%)	9 (12)		15 (10)
PR n (%)	29(40)		61(42)
nCR n (%)	7(10)		14(10)
Intent to Treat Population[c]	**n=74**		**n=148**
Median Time to Progression, months	9.4		10.4
(95% CI)	(7.6,10.6)		(8.5,11.7)
Hazard ratio (95% CI)[d]		0.839 (0.564,1.249)	
p-value[e]		0.38657	
Progression Free Survival, months	8.0		10.2
(95% CI)	(6.7,9.8)		(8.1,10.8)
Hazard ratio (95% CI)[d]		0.824 (0.574,1.183)	
p-value[e]		0.295	
1-year Overall Survival (%)[f]	76.7		72.6
(95% CI)	(64.1,85.4)		(63.1,80.0)

[a] All randomized subjects who received at least 1 non-zero dose of study medication and had measurable disease at study entry

[b] P-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in the IV arm.

[c] 222 subjects were enrolled into the study; 221 subjects were treated with VELCADE

[d] Hazards ratio estimate is based on a Cox model adjusted for stratification factors: ISS staging and number of prior lines.

[e] Log-rank test adjusted for stratification factors: ISS staging and number of prior lines.

[f] Median duration of follow up is 11.8 months

Table 22 presents a cross-tabulation summary of best response by algorithm after 4 cycles versus after 8 cycles for patients who received dexamethasone. Eighty-two subjects in the SC treatment group and 39 subjects in the IV treatment group received dexamethasone after Cycle 4.

Dexamethasone had a similar effect on improvement of response on both treatment arms:

- 30% (SC) and 30% (IV) of patients with no response at end of Cycle 4 obtained a response later.
- 13% (SC) and 13% (IV) of patients with PR at end of Cycle 4 obtained a CR later.

Table 22: Cross-tabulation of Summary of Best Response After 4 Cycles vs. After 8 Cycles for patients who received dexamethasone

	---------- Best Response After 8 Cycles ---------- (N=121)			
Treatment Group	Total	---------- Category, n (%) ----------		
Cycle 4 Best Response [a]	n (%)	CR	PR	Non-responder
IV	39 (32)	3 (8)	20 (51)	16 (41)
CR	1 (1)	1 (100)	0	0
PR	15 (12)	2 (13)	13 (87)	0
Non-responder	23 (19)	0	7 (30)	16 (70)
SC	82 (68)	8 (10)	41 (50)	33 (40)
CR	4 (3)	4 (100)	0	0
PR	31 (26)	4 (13)	27 (87)	0
Non-responder	47 (39)	0	14 (30)	33 (70)

[a] Response assessment by validated computer algorithm. This algorithm incorporates a consistent assessment of all data required for response by the modified EBMT criteria.

Relative to previously reported outcomes, the ORR after 8 cycles of treatment (52% in both treatment groups) and time to progression (median 10.4 months and 9.4 months in SC and IV treatment groups, respectively), including the effect of the addition of dexamethasone from Cycle 5 onwards, were higher than observed in prior registration study with single agent IV VELCADE (38% ORR and median TTP of 6.2 months for the VELCADE arm). Time to

Progression and ORR was also higher compared to the subgroup of patients that received only 1 prior line of therapy (43% ORR and median TTP of 7.0 months) (Table 19).

VELCADE Retreatment in Relapsed Multiple Myeloma

Study MMY-2036 (RETRIEVE) was an open-label, multicenter study designed to determine the efficacy and safety of retreatment with VELCADE in 130 patients with relapsed multiple myeloma. Patients had previously tolerated 1.0 or 1.3 mg/m^2 VELCADE alone or in combination with other agents, had CR or PR upon completion of VELCADE therapy and subsequently relapsed.

As assessed by EBMT criteria, the primary endpoint of best response was achieved in 40% of patients who had a response of PR or better including 1% of whom had a best response of CR. In these 40% of patients (n=50) who had a best response of PR or better, the median time to progression (TTP) was 8.4 months (range: 3.3 to 20.7 months). The median duration of response in these patients was 6.5 months (range: 0.6 to 19.3 months).

VELCADE Combination Treatment with Pegylated Liposomal Doxorubicin

A Phase 3 randomized, parallel-group, open-label, multicentre study (DOXIL-MMY-3001) was conducted in 646 patients comparing the safety and efficacy of VELCADE plus pegylated liposomal doxorubicin combination therapy with VELCADE monotherapy in patients with multiple myeloma who had received at least 1 prior therapy and who did not progress while receiving anthracycline-based therapy. The primary efficacy endpoint was TTP while the secondary efficacy endpoints were OS and ORR (CR+PR), using the European Group for Blood and Marrow Transplantation (EBMT) criteria.

There was a significant improvement in the primary endpoint of time to progression (TTP) for patients treated with combination therapy of VELCADE and pegylated liposomal doxorubicin. A protocol-defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45 % (95 % CI; 29-57 %), $p < 0.0001$. The median TTP was 6.5 months for the VELCADE monotherapy patients compared with 9.3 months for the VELCADE plus pegylated liposomal doxorubicin combination therapy patients. These results, though not mature, constituted the protocol-defined final analysis.

VELCADE Combination Treatment with Dexamethasone

Study MMY-2045 was a Phase 2 randomised open-label study to evaluate VELCADE in combination with dexamethasone (Vc+Dex) followed by either Vc+Dex or Vc+Dex in combination with cyclophosphamide (VDC), or lenalidomide (VDL). 163 patients with relapsed/progressive or refractory multiple myeloma were enrolled. The primary efficacy endpoint was the ORR. Secondary endpoints were changes in renal function after 4 cycles of Vc+Dex treatment, time to response, TTP, duration of response, PFS, 1-year survival, and OS.

The key efficacy results in 144 patients who received the VELCADE plus dexamethasone combination are presented in Table 23. The results demonstrate incremental benefit when compared to the previous, well-controlled VELCADE monotherapy study (APEX) and a positive effect of the combination of Vc+Dex on response rates, TTP, time to first response, PFS, and 1-year survival rate. The results are also consistent with Study MMY-3021 in which an improvement in response was seen when dexamethasone was added to VELCADE treatment in multiple myeloma patients after 4 cycles.

Table 23: Key Efficacy Results for the VELCADE plus Dexamethasone Combination (Study MMY-2045)

	Vc+Dex (N=144)
Time to Progression	N=144
Number of events (%)	72 (50.0)
Median days [months][a]	366.0 [12.0]
Progression-free Survival	N=144
Number of events (%)	85 (59.0)
Median days [months][a]	311.0 [10.2]
Overall Response Rate; n (%)	N=144
Total (CR+VGPR+PR)	101 (70.1)
CR	13 (9)
VGPR	48 (33.3)
PR	40 (27.8)

Time to First Response	N=144
Median days [months][a]	43.0 [1.4]
Duration of Overall Response	N=101
Number of events (%)	55 (54.5)
Median days [months][a]	345.0 [11.3]
Overall Survival	N=144
No. died (%)	49 (34.0)
1-year survival estimate (95% CI)	80% (73%, 87%)

CR=complete response; HR=hazard ratio; No.=number; PR=partial response; Vc=VELCADE; VGPR=very good partial response

[a] Months=days/30.4375

[b] Median overall survival was not achieved by the time of clinical cutoff for the final analysis (30 September 2011)

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma

A prospective phase 3, international, randomized (1:1), open-label clinical study [MMY-3002 (VISTA)] of 682 patients was conducted to determine whether VELCADE (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. This study included patients who were not candidates for stem cell transplant. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarized in Table 24.

Table 24: Summary of Baseline Patient and Disease Characteristics in the VISTA Study

Patient Characteristics	**VMP N=344**	**MP N=338**
Median age in years (range)	71.0 (57, 90)	71.0 (48, 91)
Gender: male/female	51% / 49%	49% / 51%

Race: Caucasian/asian/black/other	88% / 10% / 1% / 1%	87% / 11% / 2% / 0%
Karnofsky performance status score ≤70	35%	33%
Hemoglobin <100 g/L	37%	36%
Platelet count <75 x 10^9/L	<1%	1%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	64% / 24% / 8%	62% / 26% / 8%
Median β_2-microglobulin (mg/L)	4.2	4.3
Median albumin (g/L)	33.0	33.0
Creatinine clearance ≤30 mL/min [n (%)]	20 (6%)	16 (5%)

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the MP arm were offered VcMP treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up at 60.1 months. A statistically significant survival benefit in favor of the VcMP treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies that included VELCADE-based regimens. The median survival in MP treatment group has been estimated at 43.1 months, and the median survival on the VcMP treatment group has been estimated at 56.4 months. Efficacy results are presented in Table 25.

Table 25: Summary of Efficacy Analyses in the VISTA study

Efficacy Endpoint	**VMP n=344**	**MP n=338**
Time to Progression – Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24,7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	

p-value [c]	0.000002	
Progression-free Survival Events n (%)	135 (39)	190 (56)
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value [c]	0.00001	
Overall Survival[h] Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median[a] (95% CI)	56.4 mo (52.8, 60,9)	43.1 mo (35.3, 48.3)
Hazard ratio[b] (95% CI)	0.695 (0.567, 0.852)	
p-value [c]	0.00043	
Response Rate population[e] n = 668	n=337	n=331
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR + PR[f] n (%)	238 (71)	115 (35)
p-value[d]	$<10^{-10}$	
Reduction in Serum M-protein population[g] n=667	n=336	n=331

>=90% n (%)	151 (45)	34 (10)
Time to First Response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] Response Duration		
CR[f]	24.0 mo	12.8 mo
CR + PR[f]	19.9 mo	13.1 mo
Time to Next Therapy Events n (%)	224 (65.1)	260 (76.9)
Median[a] (95% CI)	27.0 mo (24.7, 31.1)	19.2 mo (17.0, 21.0)
Hazard ratio[b] (95% CI)	0.557 (0.462, 0.671)	
p-value [c]	(< 0.000001)	

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 that was performed at a median follow-up duration of 60.1 months.

[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 VMP

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

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

[e] Response population includes patients who had measurable disease at baseline

[f] EBMT criteria

[g] All randomized patients with secretory disease

[h] Survival update based on a median duration of follow-up at 60.1 months

NE: Not estimable

Previously Untreated Multiple Myeloma Patients Eligible for Autologous Stem Cell Transplantation

An integrated data analysis was conducted of three phase 3 trials (MMY-3003, IFM-2005-01, MMY-3010) to demonstrate the safety and efficacy of VELCADE, as induction therapy prior to stem cell transplantation in patients with previously untreated multiple myeloma. These studies

were similar in design (randomized, open-label, multicenter) and included 1572 patients (men and women up to 65 years of age with previously untreated multiple myeloma [Durie-Salmon stage II or III] and ECOG PS of 0 to 2/3). Patients received either a VELCADE-containing induction regimen (n=787) or a non-VELCADE-containing induction regimen (n=785). These studies evaluated VELCADE in combination with: 1) dexamethasone and adriamycin (MMY-3003), 2) thalidomide and dexamethasone (MMY-3010), or 3) dexamethasone alone (IFM-2005-01). VELCADE-containing induction regimens were compared to regimens including vincristine, adriamycin and dexamethasone or thalidomide and dexamethasone.

The VELCADE-based treatment group had improved PFS and TTP compared with the non-VELCADE-based treatment group. In addition, patients who received a VELCADE-containing induction regimen had improved post transplant and post induction response rates compared to those who received a non-VELCADE-containing induction regimen.

Integrated efficacy results from studies MMY-3003, IFM-2005-01, MMY-3010 are summarized in the following table:

Table 26: Summary of integrated efficacy of VELCADE (Vc)-based induction therapy in previously untreated multiple myeloma patients eligible for autologous stem cell transplantation

Efficacy Endpoint	**Vc-containing induction therapy n=787**	**Non-Vc-containing induction therapy n=785**
Progression-free survival		
Number assessed	787	785
Events[a] n (%)	388 (49.3)	453 (57.7)
Median (months)[a] (95% CI)	35.9 (32.8, 39.2)	28.6 (26.4, 31.7)
Hazard ratio[b](95% CI)	0.75 (0.65, 0.85)	
p-value[c]	< 0.0001	
Response Rate (Post Transplant)		
Number assessed	775	772
CR n (%)	199 (26)	106 (14)

Efficacy Endpoint	Vc-containing induction therapy n=787	Non-Vc-containing induction therapy n=785
nCR n(%)	99 (13)	76 (10)
CR + nCR n (%)	298 (38)	182 (24)
Odds ratio[d](95% CI)	2.05 (1.64, 2.56)	
p-value[e]	<0.0001	
VGPR n(%)	165 (21)	133 (17)
PR n(%)	152 (20)	211(27)
Overall response rate (CR+nCR+VGPR+PR) n(%)	615(79)	526(68)
Odds ratio[d](95% CI)	1.81 (1.43, 2.27)	
p-value[e]	<0.0001	
Response Rate (Post Induction)		
Number assessed	775	772
CR n (%)	105(14)	32 (4)
nCR n(%)	70 (9)	31 (4)
CR + nCR n (%)	175 (23)	63 (8)
Odds ratio[d](95% CI)	3.45 (2.52, 4.72)	
p-value[e]	<0.0001	
VGPR n(%)	187 (24)	76(10)
PR n(%)	284 (37)	341(44)
Overall response rate (CR+nCR+VGPR+PR) n(%)	646(83)	480(62)
Odds ratio[d](95% CI)	3.05 (2.40, 3.87)	
p-value[e]	<0.0001	

Efficacy Endpoint	Vc-containing induction therapy n=787	Non-Vc-containing induction therapy n=785
Time to Progression		
Number assessed	787	785
Events[a] n (%)	368 (46.8)	428 (54.5)
Median (months)[a](95% CI)	37.5 (35.3, 39.9)	31.3 (28.2, 33.4)
Hazard ratio[b](95% CI)	0.76 (0.66, 0.88)	
p-value[c]	0.0001	
Overall Survival		
Number assessed	787	785
Events[a] (deaths) n (%)	175 (22.2)	207 (26.4)
3-year survival rate[a](%) (95% CI)	79.7(76.4, 82.5)	74.4(70.9, 77.5)
Hazard ratio[b](95% CI)	0.81 (0.66, 0.99)	
p-value[c]	0.0402	

Note: Median follow-up duration 37 months

CI=confidence interval; CR=complete response; nCR=near complete response; VGPR= very good partial response; PR=partial response. Note: VGPR is not reported as a response category for Study MMY-3010.

[a] Based on Kaplan-Meier product limit estimates.

[b] Hazard ratio estimate is based on Cox model stratified by study. A hazard ratio less than 1 favors the Vc-containing induction therapy.

[c] Log-rank test stratified by study.

[d] Cochran-Mantel-Haenszel estimate stratified by study. An odds ratio greater than 1 favors the Vc-containing induction therapy.

[e] P-value from the Cochran Mantel-Haenszel chi-squared test.

A fourth phase 3 randomized, open-label, multicenter trial (MMY-3006) was conducted in 480 patients (men and women aged 18 to 65 years of age with previously untreated multiple myeloma). In this study, VELCADE-containing induction regimens were compared to regimens containing thalidomide and dexamethasone. The results of this study were consistent with those of the integrated analysis demonstrating improved post–induction CR+nCR rates (31% versus 11% ; p<0.0001), post transplant CR+nCR rates (55% versus 41%; p=0.0025), and a 37% reduction in the risk of disease progression or death (HR = 0.63 [95% CI: 0.45, 0.88];

p=0.0061) with the VELCADE-based induction regimen as compared with its non-VELCADE-based comparator regimen. The safety profile in the VELCADE-containing regimen was consistent with the known safety profile of VELCADE.

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 [M34103-053 (PINNACLE)] of 155 patients with progressive disease who had received at least 1 prior therapy. Velcade was administered at the recommended dose of 1.3 mg/m^2. The median number of cycles administered across all patients was 4 (range 1-17); and 8 in responding patients. Response rates to VELCADE are described in Table 27.

Table 27: Summary of Disease Outcomes in a Phase 2 Mantle Cell Lymphoma Study (PINNACLE)

[a]Response Analyses (N = 141)	N (%)	95% CI
Overall Response Rate (IWRC) (CR + CRu + PR)	47 (33)	(26, 42)
Complete Response (CR + CRu)	11 (8)	(4, 14)
CR	9 (6)	(3, 12)
Cru	2 (1)	(0, 5)
Partial Response (PR)	36 (26)	(19, 34)
Time to Event Analyses	Median	95% CI
Kaplan-Meier Estimated Duration of Response		
CR + CRu + PR (N = 47)	9.2 months	(4.9, 13.5)
CR + CRu (N = 11)	13.5 months	(13.5, NE)
Kaplan-Meier Estimated Time to Progression (N = 155)	6.2 months	(4.0, 6.9)
**Kaplan-Meier Estimated Treatment Free Interval, CR + CRu (N = 11)	13.8 months	(13.4, NE)

Median Time to Next Treatment		
CR + CRu + PR (N = 47)	12.7 months	(9.33, NE)
CR+CRu (N=11)	19.4 months	(17.8, NE)

[a]Based on International Response Workshop Criteria (IRWC).

CRu = Complete Response unconfirmed

NE=not estimable**Additional analyses

With a median duration of follow-up of more than 13 months in surviving patients, the median survival had not yet been reached and the Kaplan-Meier estimate of 1-year survival was 69%. The Kaplan-Meier estimate of 1-year survival was 94% in responders and 100% in those achieving CR or CRu.

Previously Untreated Mantle Cell Lymphoma

A randomized, open-label, Phase 3 study (LYM-3002) was conducted in 487 adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV) to determine whether VELCADE administered in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) resulted in improvement in progression free survival (PFS) when compared to the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). This clinical study utilized independent pathology confirmation and independent radiologic response assessment.

Patients in the VcR-CAP treatment arm received VELCADE (1.3 mg/m^2) administered intravenously on Days 1, 4, 8, and 11 (rest period Days 12-21); rituximab (375 mg/m^2) on Day 1; cyclophosphamide (750 mg/m^2) on Day 1; doxorubicin (50 mg/m^2) on Day 1; and prednisone (100 mg/m^2) on Day 1 through Day 5 of the 21-day treatment cycle. For patients with a response first documented at Cycle 6, two additional treatment cycles were given.

Median patient age was 66 years, 74% were male, 66% were Caucasian and 32% were Asian. 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 35% of patients had an International Prognostic Index (IPI) score of 3 (high-intermediate) and 74% had Stage IV disease. Median number of cycles received by patients in both treatment arms was 6 with 17% of patients in the R-CHOP group and 14% of subjects in the VcR-CAP group receiving up to 2 additional cycles. The majority of the patients in both groups received 6 or more cycles of treatment, 83% in the R-CHOP group and 84% in the VcR-CAP group.

The primary efficacy endpoint was progression-free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti-lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration.

The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC).

A statistically significant benefit in favor of the VcR-CAP treatment group was observed for PFS, TTP, TNT, TFI overall complete response rate, and overall survival. At a median follow-up of 40 months, a 59% improvement in the primary endpoint of PFS (Hazard Ratio [HR]=0.63; p < 0.001) was observed in the Vc-RCAP group (median=24.7 months) as compared to the R-CHOP group (median=14.4 months). The median duration of complete response was more than double in the VcR-CAP group (42.1 months) compared with the R-CHOP group (18 months) and the duration of overall response was 21.4 months longer in the VcR-CAP group. At a median follow-up of 40 months, median OS (56.3 months in the R-CHOP group, and not reached in the VcR-CAP group) favored the VcR-CAP group, (estimated HR=0.80; p=0.173). There was a trend towards prolonged overall survival favoring the VcR-CAP group; the estimated 4-year survival rate was 53.9% in the R-CHOP group and 64.4% in the VcR-CAP group.

The final analysis for OS was performed after a median follow-up of 82 months. Median OS in the VR-CAP group was 90.7 months, almost three years more than the OS achieved in the R-CHOP group, which was 55.7 months (HR=0.66; p=0.001).

Efficacy results are presented in Table 28.

Table 28: Summary of Efficacy Outcomes in a Phase 3 Mantle Cell Lymphoma Study in Previously Untreated Patients (LYM-3002)

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7)	165 (67.6)	HR[d](95% CI)=0.63 (0.50;0.79) p-value[e] < 0.001
Median[c] (95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	
Progression free survival (Investigator)[b]			
Events n (%)	128 (52.7)	179 (73.4)	

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Median[c] (95% CI) (months)	30.7 (25.1; 37.3)	16.1 (14.0; 18.4)	HR[d](95% CI)=0.51 (0.41; 0.65) p-value[e] < 0.001
Time to Progression[a]			
Events n (%)	114 (46.9)	148 (60.7)	HR[d](95% CI)=0.58 (0.45;0.74) p-value[e] < 0.001
Median[c](95% CI) (months)	30.5 (22.9; 40.9)	16.1(13.7;18.1)	
Time to Next Anti-lymphoma Therapy			
Events n (%)	94 (38.7)	145 (59.4)	HR[d] (95% CI)=0.50 (0.38;0.65) p-value[e] < 0.001
Median[c] (95% CI) (months)	44.5 (38.8; NE)	24.8 (22.1; 27.5)	
Treatment Free Interval			
n :All Treated Patients	240	242	
Events n (%)	93 (38.8)	145 (59.9)	HR[d] (95% CI)=0.50 (0.38; 0.65) p-value[e] < 0.001
Median[c] (95% CI) (months)	40.6 (33.6; NE)	20.5 (17.8; 22.8)	
Overall survival at a median follow-up of 82 months			
n :ITT patients	243	244	
Events n (%)	103 (42.4)	138 (56.6)	HR[d] (95% CI)=0.66 (0.51; 0.85) p-value[e] =0.001
Median[c](95% CI) (months)	90.7 (71.4; NE)	55.7 (47.2; 68.9)	
Response Rate			

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
n : response-evaluable patients	229	228	
Overall complete response (CR+CRu)[h] *n(%)*	122 (53.3)	95(41.7)	OR[f](95% CI)=1.688 (1.148; 2.481) p-value[g] =0.007
Overall radiological response (CR+CRu+PR)[i] *n(%)*	211 (92.1)	204 (89.5)	OR[f](95% CI)=1.428 (0.749; 2.722) p-value[g] =0.275
Response Duration			
Duration of complete response (*CR+CRu)*[j]			
n = response-evaluable patients	122	95	
Median[c] (95% CI) (months)	42.1 (30.7; 49.1)	18.0 (14.0; 23.4)	
Duration of Response (CR+CRu+PR)[k]			
n: response-evaluable subjects	211	204	
Median[c] (95% CI) (months)	36.5 (26.7; 46.7)	15.1 (12.5; 17.0)	

Note: All results are based on the analysis performed at a median follow-up duration of 40 months except for the overall survival analysis.

[a] Based on IRC assessment (radiological data only).

[b] Based on Investigator assessment.

[c] Based on Kaplan-Meier product limit estimates.

[d] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.

[e] Based on Log-rank test stratified with IPI risk and stage of disease.

[f] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and Stage of Disease as

Efficacy endpoint	VcR-CAP	R-CHOP	
n: ITT patients	243	244	

stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.

[g] P-value from the Cochran Mantel-Haenszel Chi-Squared test, with IPI and Stage of Disease as stratification factors.

[h] Include all CR + CRu, by IRC, bone marrow and LDH.

[i] Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.

[j] Calculated from first date of complete response (CR+CRu by IRC, bone marrow and LDH) to date of PD or death due to PD.

[k] Calculated from first date of response (include all radiological CR+CRu+PR by IRC) to date of PD or death due to PD.

IRC=Independent Review Committee; IPI=International Prognostic Index; LDH = Lactate dehydrogenase; CR=Complete Response; CRu= Complete response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=hazard ratio; OR= odds ratio; ITT= intent to treat; PD=Progressive disease

Patients with Previously Treated Light-Chain (AL) Amyloidosis

A Phase 1/2 study was conducted to determine the safety and efficacy of VELCADE in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular VELCADE did not exacerbate target organ damage (heart, kidney and liver). In 49 evaluable patients treated at 1.6 mg/m^2 weekly or 1.3 mg/m^2 twice weekly, a 67.3% response rate (including a 28.6% CR rate) as measured by haematological response (M- protein) was reported. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Pediatric Use

The safety and effectiveness of VELCADE in pediatric patients has not been established for multiple myeloma and mantle cell lymphoma. The safety and efficacy of VELCADE have been studied in pediatric patients with pre-B cell acute lymphoblastic leukemia (ALL). A Phase 2, single-arm efficacy, safety, and pharmacokinetic trial conducted by the Children's Oncology Group in pediatric patients with ALL assessed the activity of the addition of bortezomib to multi-agent re-induction chemotherapy. Subjects included those patients with first relapse of pre-B – cell ALL between the ages of 1 and 21-years who had relapsed within 36 months of initial diagnosis. Stratum 1 included patients with relapse within 18 months of diagnosis and stratum 2 included patients with relapse 18-36 months from diagnosis.

One hundred and four (104) patients with ALL were evaluated for safety: 7 infants less than 2 years of age, 61 children between the ages of 2 years up to 12 years, 19 adolescents between the ages of 12 years to younger than 17 years, and 17 adults between the ages of 17 and 21 years. There are no data in pediatric patients with ALL under 1 year of age.

No new safety concerns were observed when VELCADE was added to the standard pediatric pre-B cell ALL chemotherapy backbone regimen as compared with a historical control study in which the backbone regimen was given alone.

VELCADE (1.3 mg/m^2/dose) was administered twice weekly (Days 1, 4, 8, and 11) with re-induction chemotherapy during the first 35 days of treatment (Block 1). VELCADE was then given on days 1, 4, and 8 of the second 35-day treatment block (Block 2) with chemotherapy for a total of 7 VELCADE injections. VELCADE was not administered as part of the Block 3 regimen.

Re-induction Block 1	Cytarabine IT (dosage depends on age)[a] on Day 1[b] Vincristine 1.5 mg/m^2/dose IV on Days 1,8,15, 22 Doxorubicin 60 mg/m^2/dose IV on Day 1 Prednisone 20 mg/m^2/dose oral BID on Days 1-28 Pegaspargase 2500 IU/m^2/dose IM or IV on Days 2, 8, 15, and 22 Methotrexate (dosage depends on age)[c] CNS neg: IT on Days 15 and 29 CNS pos: as MTX/HC/AraC[d] IT on Days 8, 15, 22, and 29 VELCADE 1.3 mg/m^2/dose IV on Days 1, 4, 8, 11
Re-induction Block 2	Cyclophosphamide 440 mg/m^2/dose IV on Days 1-5 Etoposide 100 mg/m^2/dose IV on Days 1-5 Methotrexate (dosage depends on age)[c] CNS neg: IT on Days 1 and 22 CNS pos: as MTX/HC/AraC[d] IT on Days 1 and 22 VELCADE 1.3 mg/m^2/dose IV on Days 1, 4, 8 Filgrastim (G-CSF) 5 μg/kg/dose SC daily start on Day 6 HD Methotrexate 5000 mg/m^2/dose IV on Day 22
Re-induction Block 3	Cytarabine 3000 mg/m^2/dose every 12 hrs IV on Days 1, 2 and 8, 9 L-asparaginase 6000 IU/m^2/dose IM on Days 2, 9 Filgrastim 5 μg/kg/dose SC daily start on Day 10

Abbreviations: IT = intrathecal(ly); IV=intravenous(ly); IU = international units; BID = twice daily; IM = intramuscular(ly); CNS = central nervous system; MTX = methotrexate; HC = hydrocortisone; AraC = cytarabine; G-CSF = granulocyte colony-stimulating factor; SC = subcutaneous(ly); HD = high-dose

a. aged based dosing of cytarabine IT as follows: 1-1.99 yrs, 30 mg; 2-2.99 yrs, 50 mg; ≥ 3 yrs, 70 mg

b on Day 1 or at the time of diagnostic lumbar puncture up to 72 hrs prior to Day 1

c aged based dosing of MTX as follows: 1-1.99 yrs, 8 mg; 2-2.99 yrs, 10 mg; 3-8.99 yrs, 12 mg; ≥ 9 yrs, 15 mg

d triple therapy dosing (in mg) based on **ages** as follows:

	MTX	**HC**	**AraC**
1-1.99 yrs	8	8	16
2-2.99 yrs	10	10	20
3-8.99 yrs	12	12	24
≥ 9 yrs	15	15	30

Complete response at the end of Block 1 was evaluated in the first 60 evaluable patients to enroll in stratum 1 (n=27) and stratum 2 (n=33). In stratum 1 the CR rate was 67% (95% CI: 46, 84); the 4-month event free survival rate was 44% (95% CI: 26, 62). In stratum 2 the CR rate was 79% (95% CI: 61, 91) and the 4-month event free survival rate was 73% (95% CI: 54, 85).

Geriatric Use

No overall differences in safety or effectiveness were observed between patients ≥ age 65 and younger patients receiving VELCADE; in the patients studied with multiple myeloma and mantle cell lymphoma, but greater sensitivity of some older individuals cannot be ruled out.

5.2 Pharmacokinetic Properties

Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to eleven patients with multiple myeloma, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106ng/mL for the 1.0mg/m^2 dose and 89 to 120ng/mL for the 1.3mg/m^2 dose.

In the PK/PD substudy in Phase 3 trial, following an IV bolus or subcutaneous (SC) injection of a 1.3 mg/m^2 dose to multiple myeloma patients (n = 14 for IV, n = 17 for SC) , the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for SC and IV administration. The C_{max} after SC administration (20.4 ng/mL) was lower than IV (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 1659 liters to 3294 liters **(**489 to 1884 L/m^2**)** single- or repeat dose IV administration of 1.0mg/m^2 or 1.3mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 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 two 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 IV dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination

The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours.

Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses.

Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1.0mg/m^2 and 1.3mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0mg/m^2 and 1.3mg/m^2, respectively.

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

Special Populations

Impaired Renal Function

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 Posology and Method of Administration, 4.2)*.

Impaired Hepatic Function

The effect of hepatic impairment on the pharmacokinetics of IV bortezomib was assessed in 60 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 Table 5).

Age, Gender, Race

The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1.3 mg/m^2 doses to 104 pediatric patients (2-16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population

pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 (25%) L/hr/m^2, volume of distribution at steady-state was 834 (39%) L/m^2, and the elimination half-life was 100 (44%) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

The effects of gender and race on the pharmacokinetics of bortezomib have not been evaluated.

Drug Interactions

See section 4.5 for relevant information.

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis, Reproductive Toxicology

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.

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 0.05 mg/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.

Animal Toxicology and/or Pharmacology

See local product information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Mannitol (E421)

6.2 Incompatibilities

This product must not be mixed with other medicinal products except those mentioned in Instructions for Use/Handling.

6.3 Shelf Life

See the expiry date after the word "Expiry" on the carton.

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

6.4 Special Precautions for Storage

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

Do not store unopened vials above 30°C (86°F). Retain in original package to protect from light.

Keep out of reach of children.

6.5 Nature and Contents of Container

Five (5) or ten (10) mL, type 1, glass vial with a gray bromobutyl stopper and aluminum seal. The cap color of the 5 mL vial is green, and the cap color for the 10 mL vial is royal blue. Each vial is contained in a transparent blister pack consisting of a tray with a lid. The 5 mL vial contains 11 mg powder for solution for injection and the 10 mL vial contains 38.5 mg powder for solution for injection.

VELCADE is available in cartons containing 1 single use vial.

6.6 Instructions for Use/Handling

Administration Precautions

VELCADE is an antineoplastic. Caution should be used during handling and preparation. Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage.

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

There have been fatal cases of inadvertent intrathecal administration of VELCADE. VELCADE is for IV and subcutaneous use only**. DO NOT ADMINISTER VELCADE INTRATHECALLY.**

Reconstitution/Preparation for Intravenous and Subcutaneous Administration

The contents of each vial should be reconstituted only with normal (0.9%) saline according to the following instructions based on route of administration:

	IV		**SC**
	1 mg bortezomib	3.5 mg bortezomib	3.5 mg bortezomib
Volume of diluent (0.9% Sodium Chloride) added to reconstitute one vial	1.0 mL	3.5 mL	1.4 mL
Final Concentration after reconstitution (mg/mL)	1.0 mg/mL	1.0 mg/mL	2.5 mg/mL

The reconstituted product should be a clear and colorless solution. 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.

Procedure for Proper Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com
For any product information, please contact us at medinfosea@its.jnj.com

8. MARKETING AUTHORIZATION NUMBERS AND DATE OF AUTHORIZATION

Manufactured by	Marketing Authorization Numbers	Date of Authorization
BSP Pharmaceuticals S.P.A. Latina, Italy	1C 120/56 (N)	Initial Authorization Date: 15 October 2013 SMP Released Approval: 17 October 2017
BSP Pharmaceuticals S.P.A. Latina, Italy	1C 9/62 (N)	Initial Authorization Date: 21 April 2015 SMP Released Approval: 17 October 2017 Latest License Transfer: 8 March 2019

9. DATE OF REVISION OF THE TEXT

CCDS version 4 Aug 2023

Warning according to the announcement of Ministry of Public Health

This medicinal product may cause serious harm. It must be used only under physician's supervision.