BORTEZOMIB JUNO®

bortezomib

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BORTEZOMIB JUNO 1 mg & 3.5 mg Powder for Injection

2. QUALITITATIVE AND QUANTITATIVE COMPOSITION

BORTEZOMIB JUNO (bortezomib) is an antineoplastic agent for intravenous injection (IV) or subcutaneous (SC) use only. Each single dose vial contains:

- 1 mg of bortezomib as a sterile lyophilised powder. or
- 3.5 mg of bortezomib as a sterile lyophilised powder.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Powder for injection

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BORTEZOMIB JUNO in combination with melphalan and prednisone, is indicated for the treatment of patients with previously untreated multiple myeloma, who are not suitable for high dose chemotherapy.

BORTEZOMIB JUNO, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma

BORTEZOMIB JUNO is also indicated for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.

4.2 Dosage and administration

Recommended Dosage

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

BORTEZOMIB JUNO may be administered:

- Intravenously (at a concentration of 1 mg/mL) as a 3-5 second bolus injection or
- Subcutaneously (at a concentration of 2.5 mg/mL). **The subcutaneous route of administration is applicable to the 3.5 mg presentation only.**

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

BORTEZOMIB JUNO retreatment may be considered for multiple myeloma patients who had previously responded to treatment with BORTEZOMIB JUNO (see **CLINICAL TRIALS**).

Previously Untreated Multiple Myeloma

Transplant Eligible

1. BORTEZOMIB JUNO plus thalidomide-dexamethasone

During the induction stage, BORTEZOMIB JUNO (bortezomib) is administered twice weekly in combination with thalidomide-dexamethasone for three 3-week treatment cycles. Following stem cell transplantation, patients receive two 5-week cycles of BORTEZOMIB JUNO-thalidomide- dexamethasone. The treatment regimen is shown in **Table 1**.

Table 1: Recommended dosage regimen for BORTEZOMIB JUNO when used in combination with thalidomide and dexamethasone

Induction Therapy: Twice weekly BORTEZOMIB JUNO (3 cycles)										
Week	**1**				**2**					**3**
Vc (1.3 mg/m^2)	Day 1	--	--	Day 4	Day 8	--	--	--	Day 11	--
t (100 mg)-Cycle 1	Day 1-7				Day 8-14					--
t (200 mg)-Cycle 2-3	Day 1-7				Day 8-14					Day 15-21
d (40 mg)	Day 1	Day 2	--	Day 4	Day 5	Day 8	Day 9	--	Day 11	Day 12	--

Consolidation Therapy: Once Weekly BORTEZOMIB JUNO (2 cycles)									
Week	**1**		**2**		**3**		**4**		**5**
Vc (1.3 mg/m^2)	Day 1	--	Day 8	--	Day 15	--	Day 22	--	--
t (100 mg)	Day 1-7		Day 8-14		Day 15-21		Day 22-28		Day 29-35
d (40 mg)	Day 1	Day 2	Day 8	Day 9	Day 15	Day 16	Day 22	Day 23	--

Vc = BORTEZOMIB JUNO; t = thalidomide; d = dexamethasone

2. BORTEZOMIB JUNO plus dexamethasone

BORTEZOMIB JUNO (bortezomib) is administered as an IV injection in combination with oral dexamethasone for four 3-week treatment cycles as shown in **Table 2**.

Table 2: Recommended dosage regimen for BORTEZOMIB JUNO when used in combination with

	dexamethasone Induction Therapy: Twice weekly BORTEZOMIB JUNO (3						
Week	**cycles)** **1**		**2**				**3**
Vc (1.3 mg/m^2)	Day 1	Day 4	Day 8	--	Day 11	--	--
d (40 mg)-All Cycles	Day 1-4		--				--

Vc = BORTEZOMIB JUNO; d = dexamethasone

Non-Transplant Eligible

BORTEZOMIB JUNO (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in **Table 3**. In Cycles 1-4, BORTEZOMIB JUNO is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, BORTEZOMIB JUNO is administered once weekly (days 1, 8, 22 and 29).

Table 3: Recommended Dosage Regimen for BORTEZOMIB JUNO when used in combination with melphalan and prednisone for Patients with Previously Untreated Multiple Myeloma

Twice Weekly BORTEZOMIB JUNO (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 BORTEZOMIB JUNO (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 = BORTEZOMIB JUNO; m = melphalan, p=prednisone

Dose Management Guidelines

Dose modification and re-initiation of therapy when BORTEZOMIB JUNO 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 ANC should be ≥ 1.0 x 10^9/L
- Non-hematological toxicities should have resolved to Grade 1 or baseline

Table 4: Dose Modifications During Subsequent Cycles	
Toxicity	**Dose modification or delay**
Haematological 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 ≤30 × 10^9/L or ANC ≤0.75 x 10^9/L on a BORTEZOMIB JUNO dosing day (other than day 1)	BORTEZOMIB JUNO dose should be withheld
• If several BORTEZOMIB JUNO doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly dministration)	BORTEZOMIB JUNO 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-hAematological toxicities	BORTEZOMIB JUNO therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, BORTEZOMIB JUNO 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 BORTEZOMIB JUNO-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTEZOMIB JUNO as outlined in **Table 5**.

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

Table 5: Recommended Dose Modification for BORTEZOMIB JUNO-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy.	
Severity of Peripheral Neuropathy Signs and Symptoms*	**Modification of Dose and Regimen**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting Instrumental Activities of Daily Living (ADL)**)	Reduce BORTEZOMIB JUNO to 1.0 mg/m^2 OR Change BORTEZOMIB JUNO treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)***)	Withhold BORTEZOMIB JUNO therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of BORTEZOMIB JUNO at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue BORTEZOMIB JUNO

* Grading based on NCI Common Toxicity Criteria

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

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

Relapsed / Refractory Multiple Myeloma

The recommended dose of BORTEZOMIB JUNO is 1.3 mg/m^2/dose administered twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of BORTEZOMIB JUNO.

It is recommended that patients with a confirmed complete response receive 2 additional cycles of BORTEZOMIB JUNO beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of BORTEZOMIB JUNO therapy.

For extended therapy of more than 8 cycles, BORTEZOMIB JUNO may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (days 1, 8, 15, and 22) followed by a 13-day rest period (days 23 to 35) (see **CLINICAL TRIALS** for a summary of dose administration during clinical trials).

Dose Modification and Reinitiation of Therapy

BORTEZOMIB JUNO therapy should be withheld at the onset of any Grade 3 non-haematological or Grade 4 haematological toxicities excluding neuropathy as discussed below (see **section 4.4**). Once the symptoms of the toxicity have resolved, BORTEZOMIB JUNO 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). **Table 5** above contains the recommended dose modification for the management of patients who experience BORTEZOMIB JUNO-related neuropathic pain and/or peripheral sensory neuropathy. Severe autonomic neuropathy resulting in treatment interruption or discontinuation has been reported. Patients with pre-existing severe neuropathy should be treated with BORTEZOMIB JUNO only after careful risk/benefit assessment.

Retreatment for Multiple Myeloma

Patients who have previously responded to treatment with BORTEZOMIB JUNO (either alone or in combination) and who have relapsed should be started on retreatment at the last tolerated dose.

Patients with Renal Impairment

The pharmacokinetics of BORTEZOMIB JUNO are not influenced by the degree of renal impairment. Therefore, dosing adjustments of BORTEZOMIB JUNO are not necessary for patients with renal insufficiency. Since dialysis may reduce BORTEZOMIB JUNO concentrations, the drug should be administered after the dialysis procedure (see **section 5.2**).

Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended BORTEZOMIB JUNO dose. Patients with moderate or severe hepatic impairment should be started on BORTEZOMIB JUNO at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance (see **Table 6**).

Table 6: Recommended Starting Dose Modification for BORTEZOMIB JUNO in Patients with Hepatic Impairments

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

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

Administration

Intravenous injection (IV)

BORTEZOMIB JUNO 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.

Subcutaneous injection (SC)

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 BORTEZOMIB JUNO injection subcutaneously, a less concentrated BORTEZOMIB JUNO solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously or change to IV injection.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Overall treatment with bortezomib must be done under the supervision of a physician, however administration of the drug product may be done by a healthcare professional experienced in the administration of oncology medications.

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib is for IV or SC use only**. DO NOT ADMINISTER BORTEZOMIB INTRATHECALLY.**

Overall, the safety profile of patients treated with bortezomib in monotherapy was similar to that

observed in patients treated with bortezomib in combination with melphalan and prednisone.

Peripheral Neuropathy

Bortezomib 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 burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening (including ≥ Grade 3) during treatment with bortezomib. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperaesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness.

In the Phase 3 study comparing bortezomib 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). Therefore, patients with pre-existing PN or at high risk of peripheral neuropathy may benefit from starting bortezomib subcutaneously.

Patients experiencing new or worsening peripheral neuropathy may require a change in dose, schedule or route of administration to SC (see **section 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 phase III multiple myeloma (APEX) study of bortezomib IV 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 II studies (see **section 4.8**).

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.

Hypotension

Patients developing orthostatic hypotension on bortezomib did not have evidence of orthostatic hypotension prior to treatment with bortezomib. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of bortezomib.

In phase II studies and the APEX study, 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 receiving medications known to be associated with hypotension and with patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids and/or sympathomimetics (see **section 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 an existing heart disease should be closely monitored. In the phase III (APEX) study of bortezomib IV 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 bortezomib and dexamethasone groups, 5% and 4%, respectively. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

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 bortezomib. 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 bortezomib for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy.

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Seizures

Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

Laboratory Tests

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

Thrombocytopenia

Bortezomib treatment is associated with thrombocytopenia (see **section 4.8**). Platelet counts were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. On average, the pattern of platelet count decrease and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pre-treatment platelet count is shown in **Table 7** for the APEX study. In the phase III (APEX) study of bortezomib IV vs. dexamethasone, the incidence of significant bleeding events (≥ Grade 3) was similar on both the bortezomib (4%) and dexamethasone (5%) arms. Platelet counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be held when the platelet count is <25,000/μL and reinitiated at a reduced dose after resolution (see **sections 4.2** and **4.8**). Transfusions may be used at the discretion of the physician. There have been reports of gastrointestinal and intracerebral haemorrhage in association with Bortezomib.

Table 7: The Severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the APEX study

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

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

Thrombocytopenia was reported in 43% of patients in the phase II studies.

Gastrointestinal Adverse Events

Bortezomib treatment can cause nausea, diarrhoea, constipation and vomiting (see **section 4.8**) sometimes requiring use of antiemetics and antidiarrhoeals. Fluid and electrolyte replacement should be administered to prevent dehydration. Since patients receiving bortezomib therapy may experience vomiting and/or diarrhoea, 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.

Tumour Lysis Syndrome

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

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 bortezomib. There is limited re-challenge information in these patients.

Patients with Hepatic Impairment

Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment. Patients with moderate and severe hepatic impairment should be treated with caution at reduced starting doses of bortezomib and closely monitored for toxicities (see **section 4.2** and **5.2**).

4.5 Interactions with other medicines and other forms of interactions

In vitro and animal *ex vivo* studies indicate that bortezomib is a weak inhibitor of cytochrome P450 (CYP) isoenzymes, 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 CYP3A inhibitor) on the pharmacokinetics of IV bortezomib, 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 IV bortezomib, 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 bortezomib showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. The concomitant use of bortezomib with strong CYP3A4 inducers is not recommended, as efficacy may be reduced. Examples of CYP-3A4 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 bortezomib showed a 17% increase in mean bortezomib AUC based on data from 21 patients. This is not considered clinically relevant.

During clinical trials, hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic agents receiving bortezomib 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.

Effects on Laboratory Tests

None known.

4.6 Fertility, pregnancy & lactation

Use in Pregnancy

Category C

Women of child bearing potential should avoid becoming pregnant while being treated with bortezomib. The placental transfer of bortezomib is unknown, but any occurrence may disrupt cycling in the developing fetus, although teratogenicity was not observed in rats and rabbits at maximum tolerated doses.

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (approximately 0.5 mg/m^2/day) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m^2 based on body surface area and calculated on a single-dose basis. Increased post-implantation loss and reduced foetal weights were seen in rabbits at the highest dose tested, which was a maternally toxic dose. Litter values were unaffected by a non-maternotoxic dose (approximately 0.3 mg/m^2/day).

No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If bortezomib is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the foetus.

Patients should be advised to use effective contraceptive measures to prevent pregnancy.

Use in Lactation

It is not known whether bortezomib or its metabolites are excreted in animal or human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-fed infants from bortezomib, women should be advised against breast-feeding while being treated with bortezomib.

4.7 Effect on ability to drive and use machines

Bortezomib 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

Adverse events

Summary of Clinical Trials of bortezomib IV in patients with previously untreated multiple myeloma:

Results from the GIMEMA and IFM2005 studies

The following table describes the safety data from the GIMEMA and IFM2005 studies in patients with previously untreated multiple myeloma who were eligible for autologous stem cell transplantation, and received bortezomib (1.3 mg/m^2) in combination with thalidomide (100 mg, then 200 mg) and dexamethasone (40 mg) in the GIMEMA study, or dexamethasone (40 mg) in the IFM2005 study.

Table 8: Adverse events following induction in randomised controlled studies GIMEMA and

IFM2005

Adverse event, n (%)	GIMEMA		IFM2005	
	VcTD n=236	TD n=238	VcD n=239	VAD n=239
Any adverse event	nr	nr	231 (96.7)*	219 (91.6)*
Any serious adverse event	31 (13.1)	30 (12.6)	65 (27.2)	81 (33.9)
Any grade 3 or 4 adverse event	132 (55.9)	79 (33.1)	112 (46.9)	110 (46.0)
Any grade 3 or 4 non-haematologic adverse event	120 (50.8)	73 (30.6)	nr	nr
Skin rash	24 (10.1)	4 (1.6)	0 (0)	0 (0)
Peripheral neuropathy	23 (9.7)	5 (2.1)	17 (7.1)	5 (2.1)
Deep vein thrombosis	8 (3.3)	12 (5.0)	nr	nr
Constipation	10 (4.2)	7 (2.9)	nr	nr
Infections	nr	nr	21 (8.8)	29 (12.1)
Infections excluding herpes zoster	7 (2.9)	11 (4.6)	nr	nr
Herpes zoster (all grades)	nr	nr	22 (9.2)	5 (2.1)
Gastrointestinal events (excluding constipation where individually reported)	5 (2.1)	1 (0.4)	0 (0)	0 (0)
Cardiac toxicity	5 (2.1)	5 (2.1)	0 (0)	0 (0)
Liver toxicity	4 (1.6)	7 (2.9)	nr	nr
Fatigue	nr	nr	0 (0)	0 (0)
Pneumonia	nr	nr	nr	nr
Any grade 3 or 4 haematologic adverse event	nr	nr	nr	nr
Anaemia	nr	nr	10 (4.2)*	21 (8.8)*
Neutropaenia	nr	nr	12 (5.0)*	24 (10.0)*
Thrombocytopenia	nr	nr	7 (2.9)	3 (1.3)
Thrombosis	nr	nr	4 (1.7)*	13 (5.4)*
Discontinued during or after induction therapy	13 (5.5)	26 (10.9)	44 (18.4)	32 (13.4)
Adverse event leading to death	1 (0.4)	0 (0)	0 (0)*	7 (2.9)*

* $p < 0.05$ for comparison of AE rate between VcD and VADVcTD: bortezomib-thalidomide-dexamethasone; TD: thalidomide-dexamethasone; VcD: bortezomib-dexamethasone; VAD: vincristine-doxorubicine-dexamethasone.

During consolidation therapy of the GIMEMA study, grade 3-4 adverse events were similar to those reported during induction, although rates were much lower. Notably, the rate of grade 3-4 peripheral neuropathy was 1.2% with VcTD consolidation.

Results from the VISTA study

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

Table 9: Treatment Emergent Drug Related Adverse Events reported in ≥ 10% of patients treated with bortezomib IV in combination with melphalan and prednisone

	VcMP (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)

	---------- VcMP ---------- (n=340)			---------- MP ---------- (n=337)		
MedDRA System Organ Class Preferred Term	Total n (%)	Toxicity Grade, n (%) 3	≥4	Total n (%)	Toxicity Grade, n (%) 3	≥4
Anaemia	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
Diarrhoea	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
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 bortezomib. In the VISTA 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 administrated 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. Similar results were observed during the IFM2005 study; herpes zoster was more common in patients treated with bortezomib-based regimen compared to control regimen. During consolidation, the GIMEMA study reported similar rates (0.6%) of grade 3-4 incidences of herpes zoster between the two study arms (p=1.0000).

Summary of Clinical Trials of bortezomib IV in patients with relapsed/refractory multiple myeloma:

The adverse events most commonly reported, regardless of causality, in the APEX study in relapsed / refractory multiple myeloma patients (see **CLINICAL TRIALS**) are presented in **Table 10**. All adverse events occurring at ≥10% are included.

Table 10: Most Commonly Reported (≥10% in bortezomib arm) Adverse Events in the APEX study using the 1.3 mg/m^2 dose (N=663)						
	Bortezomib (N=331)			Dexamethasone (N=332)		
	All Events %	Grade 3 %	Grade 4 %	All Events %	Grade 3 %	Grade 4 %
Adverse Event	**100**	**61**	**14**	**98**	**44**	**16**
Body as a Whole-General Disorders						
Asthenic conditions (fatigue, malaise, weakness)	61	12	<1	45	6	0
Pyrexia	35	2	0	16	1	<1
Rigors	11	0	0	2	0	0
Oedema lower limb	11	0	0	13	<1	0
Gastro-Intestinal System Disorders						
Diarrhea	57	7	0	21	2	0
Nausea	57	2	0	14	0	0
Constipation	42	2	0	15	1	0
Vomiting	35	3	0	6	1	0
Abdominal pain	16	2	0	4	<1	0
Central & Peripheral Nervous System Disorders						
Peripheral Neuropathy*	36	7	<1	9	<1	<1
Paresthesia and dysesthesia	27	2	0	11	<1	0
Headache	26	<1	0	13	<1	0
Dizziness (excluding vertigo)	14	<1	0	10	0	0
Blood and lymphatic system disorders						
Thrombocytopenia	35	26	4	11	5	1
Anemia	26	9	<1	22	10	<1
Neutropenia	19	12	2	2	1	0
Psychiatric disorders						
General	35	3	<1	49	5	1
Insomnia	18	<1	0	27	2	0
Metabolic and Nutritional Disorders						
Appetite decreased and anorexia	34	3	0	9	<1	0
Respiratory System disorders						
Cough	21	<1	0	11	<1	0
Dyspnoea	20	5	<1	17	3	<1
Skin and subcutaneous tissue disorders						
Rash	18	1	0	6	0	0
Infections and infestations						
Lower respiratory/lung infections	15	4	<1	21	5	<1
Nasopharyngitis	14	<1	0	7	0	0
Herpes zoster	13	2	0	5	1	<1
Musculoskeletal and connective tissue disorders						
Bone pain	16	4	0	15	3	0
Pain in limb	15	2	0	7	<1	0
Back pain	14	3	0	10	1	0
Arthralgia	14	<1	0	11	2	0
Muscle cramps	12	0	0	15	<1	0
Myalgia	12	<1	0	5	<1	0

*Peripheral neuropathy includes all terms under peripheral neuropathy not elsewhere classified (NEC), (Peripheral neuropathy not otherwise specified (NOS), peripheral neuropathy aggravated, peripheral sensory neuropathy and peripheral motor neuropathy and neuropathy NOS).

Summary of Clinical Trials of bortezomib IV vs. SC in patients with relapsed multiple myeloma:

The safety and efficacy of bortezomib SC were evaluated in one Phase III study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of bortezomib IV vs. SC in 222 patients with relapsed multiple myeloma.

Table 11: Incidence of bortezomib Adverse Drug Reactions reported in ≥ 10% of patients in the Phase 3 Relapsed Multiple Myeloma Study comparing bortezomib IV and SC

	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
Blood and lymphatic system disorders						
Anaemia	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
Diarrhoea	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						
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						
Dyspnoea	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 12: Incidence of Adverse Drug Reactions with >10% Difference in Overall Incidence between Treatment Arms in the Phase 3 Relapsed Multiple Myeloma Study comparing bortezomib 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						
Diarrhoea (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 NEC	39 (53)	12 (16)	10 (14)	56 (38)	9 (6)	9 (6)

TEAE = Treatment Emergent Adverse Event

G ≥ 3 = Toxicity Grade greater than equal to 3

Disc = Discontinuation of any study drug.

Patients who received bortezomib 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; *p*-value is 0.0784), and a 5% lower incidence of discontinuation of bortezomib (22% vs 27%; *p*-value is 0.5052). The overall incidence of diarrhoea (24% for the SC arm vs 36% for the IV arm; *p*-value is 0.0572), gastrointestinal and abdominal pain (6% for the SC arm vs 19% for the IV arm; *p*-value is 0.0049), asthenic conditions (27% for SC arm vs 39% for IV arm), upper respiratory tract infections (14% SC arm vs 26% IV arm; *p*-value is 0.0903) and peripheral neuropathy NEC (38% SC arm vs 53% IV arm; *p*-value is 0.0444) 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; *p*-value is 0.0264), and the discontinuation rate due to peripheral neuropathies was 8% lower for the subcutaneous group (5%) as compared to the intravenous group (14%); *p*-value is 0.0771.

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 (bortezomib treatment modification based on local reactions was needed in 2 subjects (1 treatment discontinuation; 1 drug withholding and reduction in study drug concentration from 2.5 mg/mL to 1 mg/mL).

Bortezomib 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 bortezomib IV (Study MMY-2036).

Table 13: Incidence of bortezomib Adverse Drug Reactions reported in ≥ 10% of patients (Study MMY-2036)

	Vc Retreatment (MMY-2036)

	Total	Toxicity Grade 3	Toxicity Grade ≥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)
Anaemia	48 (37)	5 (4)	1 (1)
Neutropenia	23 (18)	9 (7)	0
Leukopenia	20 (15)	5 (4)	0
Gastrointestinal disorders			
Diarrhoea	45 (35)	9 (7)	0
Constipation	36 (28)	0	0
Nausea	14 (11)	0	0
General disorders and administration site conditions			
Pyrexia	31 (24)	2 (2)	0
Asthenia	29 (22)	6 (5)	0
Fatigue	21 (16)	0	0
Oedema 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
Dyspnoea	14 (11)	1 (1)	0

Key: Vc = bortezomib; 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.

Serious Adverse Events (SAEs)

In the APEX study, 44% of patients from the bortezomib treatment arm experienced a SAE during the study, as did 43% of dexamethasone-treated patients. The most commonly reported SAEs in the bortezomib treatment arm were pyrexia (6%), diarrhoea (5%), dysponea and pneumonia (4%) and vomiting (3%). In the dexamethasone group, the most common SAEs were pneumonia (7%), pyrexia (4%) and hyperglycaemia (3%). Twenty five percent (25%) and 18% of bortezomib and dexamethasone patients respectively were discontinued from treatment due to adverse events assessed as drug related by the investigators. The most common for bortezomib discontinuation was peripheral neuropathy (8%) and for dexamethasone was psychotic disorder and hyperglycaemia (2% each).

In the APEX study, 4 deaths were considered to be bortezomib-related: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four (4) deaths were considered dexamethasone–related: 2 cases of sepsis, 1 case of bacterial meningitis and 1 case of sudden death at home. In the phase II studies 2 deaths were reported and considered by the investigator to be possibly related to bortezomib: 1 case of cardiopulmonary arrest and 1 case of respiratory failure.

Adverse reactions

The following adverse reactions were considered to have at least a possible or probable causal relationship to bortezomib by the investigators during 5 non-comparative phase II studies and 1 comparative phase III trial (APEX) in 663 patients with relapsed or refractory multiple myeloma, of whom 331 received bortezomib as single agent. The safety database comprises data from patients with multiple myeloma or B-cell lymphocytic leukaemia. Patients were treated with bortezomib as a single agent, or in combination with dexamethasone.

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Infections and infestations

Common: herpes zoster, pneumonia, bronchitis, sinusitis, nasopharyngitis, herpes simplex.

Uncommon: candidal infection, gastroenteritis, upper and lower respiratory tract infection, infection, influenza, fungal infection, sepsis, urinary tract infection, catheter related infection, haemophilus infection, pneumonia pneumococcal, post herpetic neuralgia, bacteraemia, blepharitis, bronchopneumonia, cytomegalovirus infection, infectious mononucleosis, varicella, oral candidiasis, pleural infection.

Blood and lymphatic system disorders

Very Common: thrombocytopenia (see **section 4.4**), anaemia, neutropenia.

Common: leukopenia, lymphopenia.

Uncommon: lymphadenopathy, febrile neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenic purpura.

Immune system disorders

Uncommon: hypersensitivity, immunocomplex mediated hypersensitivity.

Metabolism and nutrition disorders

Very Common: appetite decreased.

Common: dehydration, hyperglycaemia, hypokalaemia.

Uncommon: hypercalcaemia, hyperkalaemia, hyperuricaemia, hyponatraemia, hypernatraemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia, hypoglycaemia, appetite increased, cachexia, vitamin B12 deficiency, tumour lysis syndrome (see **section 4.4**).

Endocrine disorders

Uncommon: Inappropriate antidiuretic hormone (ADH) secretion.

Psychiatric disorders

Common: insomnia, anxiety, confusion, depression.

Uncommon: agitation, delirium, restlessness, mood swings, mental status changes, sleep disorder, irritability, hallucinations, abnormal dreams.

Nervous system disorders

Very Common: peripheral neuropathy, peripheral sensory neuropathy (see **section 4.4**), headache, paraesthesia.

Common: dizziness (excluding vertigo), dysgeusia, peripheral neuropathy aggravated, polyneuropathy, dysaesthesia, hypoaesthesia, tremor.

Uncommon: convulsions, syncope, disturbance in attention, increased activity, ageusia, somnolence, migraine, peripheral motor neuropathy, jerky movements, dizziness postural, sciatica, cognitive disorder, mononeuropathy, paresis, restless leg syndrome, speech disorder, intracranial haemorrhage, paraplegia, subarachnoid haemorrhage.

Eye disorders

Common: vision blurred (see **section 4.4**), eye pain.

Uncommon: dry eye, conjunctivitis, eye discharge, vision abnormal, eye haemorrhage,

photophobia, eye irritation, lacrimation increased, conjunctival hyperaemia, eye swelling.

Ear and labyrinth disorders

Common: vertigo.

Uncommon: tinnitus, deafness, hypoacusis, hearing impaired.

Cardiac disorders

Uncommon: Development or exacerbation of congestive heart failure (see **PRECAUTIONS**), cardiac failure, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, cardiac arrest, cardiogenic shock, tachycardia, sinus tachycardia, supraventricular tachycardia, arrhythmia, atrial fibrillation, palpitations, sinus arrest, atrioventricular block complete, angina pectoris, angina unstable, myocardial infarction.

Rare: New onset of decreased left ventricular ejection fraction.

Vascular disorders

Common: hypotension, orthostatic and postural hypotension (see **section 4.4**), phlebitis, haematoma, hypertension.

Uncommon: flushing, petechiae, hot flushes, ecchymosis, purpura, cerebral hemorrhage, vasculitis, vein discolouration, vein distended, wound hemorrhage, pulmonary hypertension, cerebrovascular accident.

Respiratory, thoracic and mediastinal disorders

Very Common: dyspnoea.

Common: epistaxis, dyspnoea exertional, cough, rhinorrhoea.

Uncommon: nasal congestion, wheezing, pleural effusion, hoarseness, chest wall pain, hypoxia, pulmonary congestion, rhinitis, asthma, hyperventilation, orthopnoea, sinus pain, throat tightness, productive cough, respiratory alkalosis, respiratory arrest, tachypnoea.

Gastrointestinal disorders (see **section 4.4**)

Very Common: nausea, diarrhoea, vomiting, constipation.

Common: abdominal pain, dyspepsia, loose stools, abdominal pain upper, flatulence, abdominal distension, hiccups, mouth ulceration, pharyngolaryngeal pain, stomatitis, dry mouth.

Uncommon: ileus paralytic, abdominal discomfort, eructation, gastrointestinal motility disorder, oral pain, retching, antibiotic associated colitis, change in bowel habit, diarrhoea haemorrhagic, gastrointestinal haemorrhage, spleen pain, colitis, dysphagia, oesophagitis, gastritis, gastro-oesophageal reflux disease, gastrointestinal pain, gingival bleeding, gingival pain, haematemesis, hiatus hernia, irritable bowel syndrome, oral mucosal petechiae, rectal haemorrhage, salivary hypersecretion, tongue coated, tongue discolouration, enteritis, faecal impaction, acute pancreatitis.

Hepatobiliary disorders (see **section 4.4**)

Uncommon: hyperbilirubinaemia, hepatitis, hepatic haemorrhage, hypoproteinaemia

Skin and subcutaneous tissue disorders

Very Common: rash.

Common: pruritus, erythema, periorbital oedema, urticaria, rash pruritic, sweating increased, dry skin, eczema.

Uncommon: night sweats, rash erythematous, alopecia, contusion, pruritus generalised, rash macular, rash papular, skin nodule, rash generalized, dermatitis, eyelid oedema, nail disorder, photosensitivity reaction, skin discolouration, dermatitis atopic, hair texture abnormal, heat rash, psoriasis, vasculitic rash, face oedema, pressure sore, ichthyosis.

Musculoskeletal and connective tissue disorders

Very Common: myalgia.

Common: pain in limb, muscle cramps, arthralgia, bone pain, peripheral swelling, muscle weakness, back pain, musculoskeletal pain.

Uncommon: joint stiffness, buttock pain, joint swelling, muscle spasms, muscle twitching or sensation of heaviness, muscle stiffness, swelling, pain in jaw.

Renal and urinary disorders

Common: renal impairment, dysuria.

Uncommon: renal failure acute, renal colic, haematuria, proteinuria, urinary frequency, difficulty in micturition, renal failure, oliguria, urinary retention, loin pain, urinary incontinence, micturition urgency.

General disorders and administration site conditions

Very Common: fatigue (see **section 4.4**), pyrexia.

Common: weakness, rigors, malaise, influenza like illness, oedema peripheral, pain, lethargy, oedema, chest pain, asthenia.

Uncommon: fall, mucosal inflammation, feeling cold, chest pressure sensation, injection site phlebitis, mucosal haemorrhage, tenderness, injection site erythema, neuralgia, chest discomfort, groin pain, chest tightness, extravasation inflammation.

Investigations

Common: weight decreased, blood lactate dehydrogenase increased.

Uncommon: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, blood urea increased, gamma-glutamyltransferase increased, blood amylase increased, blood bilirubin increased, blood phosphate decreased, liver function tests abnormal, red blood cell count decreased, weight increased, white blood cell count decreased, blood bicarbonate decreased, heart rate irregular, C-reactive protein increased.

Injury, poisoning and procedural complications

Uncommon: catheter related complications, post procedural pain, post procedural haemorrhage, burns.

Reproductive system and breast disorders

Uncommon: testicular pain, erectile dysfunction.

Potentially immunocomplex-mediated reactions (see **section 4.4**)

Uncommon: potentially immunocomplex-mediated reactions, such as serum-sickness –type reaction, polyarthritis with rash and proliferative glomerulonephritis.

Post Marketing Experience

Clinically significant adverse reactions are listed if they have been reported during post approval use of bortezomib and have not been reported in clinical trials:

Blood and lymphatic system disorders

Rare: disseminated intravascular coagulation.

Very rare: thrombotic microangiopathy

Cardiac Disorders

Rare: atrioventricular block complete, cardiac tamponade.

Ear and labyrinth disorders

Rare: deafness bilateral.

Eye Disorders

Rare: ophthalmic herpes, optic neuropathy and blindness, chalazion/blepharitis.

Gastrointestinal disorders

Uncommon: intestinal obstruction

Rare: ischemic colitis, acute pancreatitis.

Hepatobiliary disorders

Rare: liver failure

Infections and infestations

Rare: herpes meningoencephalitis, septic shock

Very Rare: Progressive multifocal leukoencephalopathy[a]

Immune System Disorders

Rare: angioedema

Very rare: anaphylactic reaction

Nervous system disorders

Rare: encephalopathy, autonomic neuropathy, posterior reversible encephalopathy syndrome.

Respiratory, thoracic and mediastinal disorders

Rare: acute diffuse infiltrative pulmonary disease (see **section 4.4**)

pulmonary hypertension

Skin and subcutaneous tissue disorders

Rare: acute febrile neutrophilic dermatosis (Sweet's syndrome).

Very Rare: Stevens-Johnson Syndrome and toxic epidermal necrolysis

[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 bortezomib.

4.9 Overdose

Cardiovascular safety pharmacology studies in monkeys and dogs showed 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 ionotropic or pressor agents. In dog studies, a slight increase in the corrected QT interval was observed at a lethal dose.

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

There is no known specific antidote for bortezomib overdosage. In the event of overdosage, patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or ionotropic agents) and body temperature (see **sections 4.2** and **4.4**).

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 signalling 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 tumour growth *in vivo* in nonclinical tumour models, including multiple myeloma.

Data from *in vitro*, *ex-vivo*, and animal models with bortezomib suggest that it increases osteoblast differentiation and acitivity 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 trials

All response and progression data listed below for both previously untreated multiple myeloma in non-transplant eligible patients and relapsed / refractory multiple myeloma were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. The response and progression data for transplant-eligible multiple myeloma patients were assessed using the International Myeloma Working Group (IMWG) criteria.

Previously Untreated Multiple Myeloma

- Transplant Eligible

The safety and efficacy of bortezomib, as induction therapy prior to stem cell transplantation in previously untreated multiple myeloma patients, has been assessed in multiple Phase III and Phase II trials.

A Phase III, randomised (1:1), open-label, multi-centre study conducted by the Italian Myeloma Network - GIMEMA, randomised 480 transplant-eligible patients under the age of 65 to receive three 3-week cycles of bortezomib (1.3 mg/m^2, days 1, 4, 8, 11) in combination with thalidomide (100 mg, days 1-14 in cycle 1, then 200 mg daily) and dexamethasone (40 mg, days 1, 2, 4, 5, 8, 9, 11, 12) (Vc-TD), or thalidomide and dexamethasone (TD) prior to tandem autologous transplant. Three months following transplant, patients received two cycles of consolidation treatment; patients randomized to receive Vc-TD induction received two 35-day cycles of bortezomib (1.3 mg/m^2, days 1, 8, 15, 22), thalidomide (100 mg daily) and dexamethasone (40 mg, days 1, 2, 8, 9, 15, 16, 22, 23) consolidation; patients randomized to receive thalidomide-dexamethasone induction received two 35-day cycles of thalidomide-dexamethasone consolidation. The primary endpoint of the study was response rate ≥nCR following induction therapy.

Patients randomized to Vc-TD arm achieved significantly higher rates of complete plus near complete response and very good partial response or better, compared to the thalidomide-dexamethasone arm following induction treatment. This difference was maintained following both transplant and consolidation therapy. Response rates are presented in **Table 14**.

Table 14: Summary of Response Rates by IMWG criteria in the GIMEMA study

Response Rate n (%)	Vc-TD n=236	TD n=238	*p*-value
Post-induction Therapy*			
CR	44 (19)	11 (5)	<0.0001
CR+nCR**	73 (31)	27 (11)	<0.0001
≥VGPR	146 (62)	66 (28)	<0.0001
≥PR	220 (93)	187 (79)	<0.0001
MR/SD	16 (7)	39 (16)	0.0011
PD	0	12 (5)	0.0005
Post-first ASCT			
CR	89 (38)	54 (23)	0.0004
CR+nCR	123 (52)	74 (31)	<0.0001
≥VGPR	186 (79)	137 (58)	<0.0001
≥PR	220 (93)	201 (84)	0.0025
MR/SD	15 (6)	20 (8)	0.3941
PD	1 (0)	17 (7)	0.0001
Post-second ASCT			
CR	98 (42)	72 (30)	0.0105
CR+nCR	130 (55)	98 (41)	0.0024
≥VGPR	193 (82)	152 (64)	<0.0001
≥PR	220 (93)	199 (84)	0.0011
MR/SD	14 (6)	19 (8)	0.3804
PD	2 (1)	20 (8)	0.0001
Post-consolidation			
CR	116 (49)	82 (35)	0.0012
CR+nCR	147 (62)	108 (45)	0.0002
≥VGPR	201 (85)	162 (68)	<0.0001
≥PR	218 (92)	201 (84)	0.0071
MR/SD	12 (5)	16 (7)	0.4495
PD	6 (3)	21 (9)	0.0032
Best overall response			
CR	136 (58)	97 (41)	0.0001
CR+nCR	168 (71)	128 (54)	<0.0001
≥VGPR	210 (89)	175 (73.5)	<0.0001
≥PR	227 (96)	212 (89)	0.0074

* Similar differences in post-induction response rates were reported by study investigators (CR+nCR: 32% vs. 13%, *p*<0.0001). Differences in RR following transplantation and consolidation by investigator assessment were also similar to those centrally assessed.

** These significant differences in CR+nCR rates between arms were maintained following cyclophosphamide to collect peripheral blood stem cells (42% vs 21%, *p*<0.0001).

ASCT: autologous stem cell transplantation; CR: complete response; MR: minimal response; nCR: near-complete response; PD: progressive disease; PR: partial disease; SD: stable disease; TD = thalidomide-dexamethasone; VGPR: very good partial response; Vc-TD: bortezomib-thalidomide-dexamethasone

In addition, compared with the TD arm, Progression Free Survival (PFS) was also significantly longer for patients randomized to the Vc-TD arm (HR, 0.629 [CI: 0.451-0.878], *p*=0.0061). The estimated 3-year PFS rate was 68% in the VTD arm and 56% in TD (*p*=0.0057) (see **Figure 1**). 58 (24.5%) and 86 (36%) patients progressed or died, respectively. The estimated 3-year probability of progression or relapse was 29% in the Vc-TD versus 39% in the TD arm (HR, 0.609 [CI: 0.425-0.873], *p*=0.0073; *p*=0.0061 by Kaplan-Meier analysis) (see **Figure 2**).

Figure 1: Progression-Free Survival Study GIMEMA: All Randomised Subjects Analysis Set)

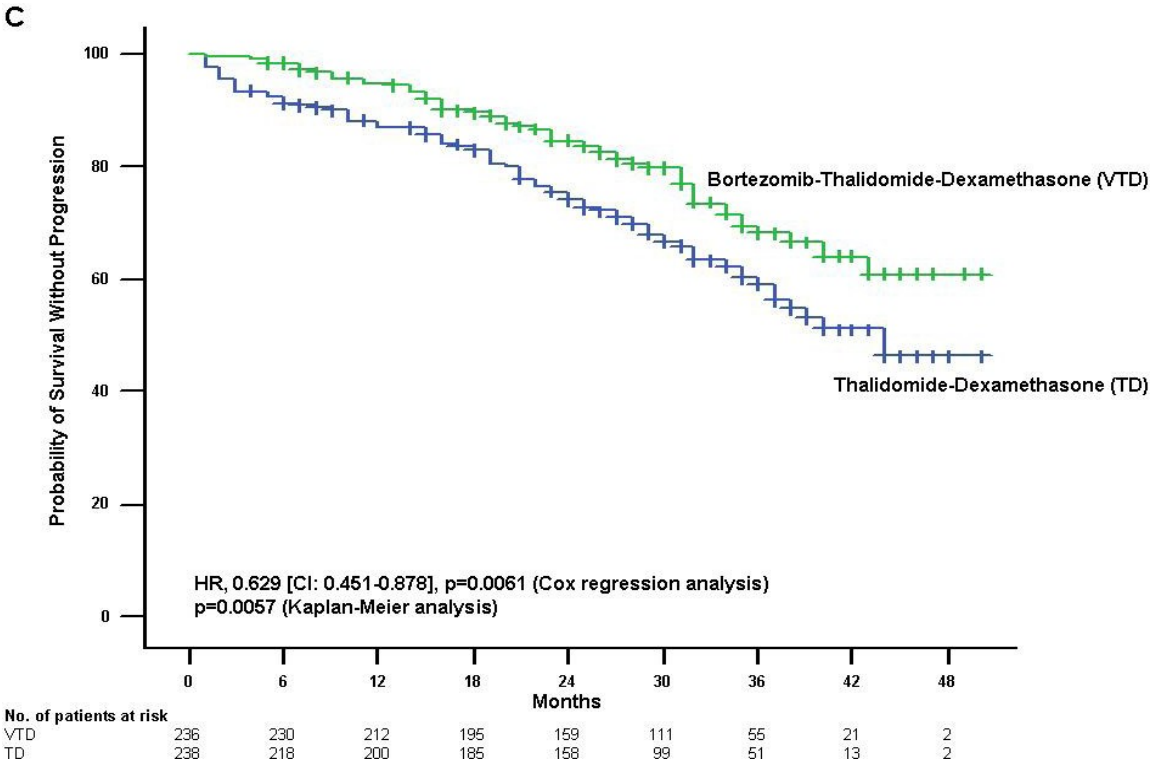
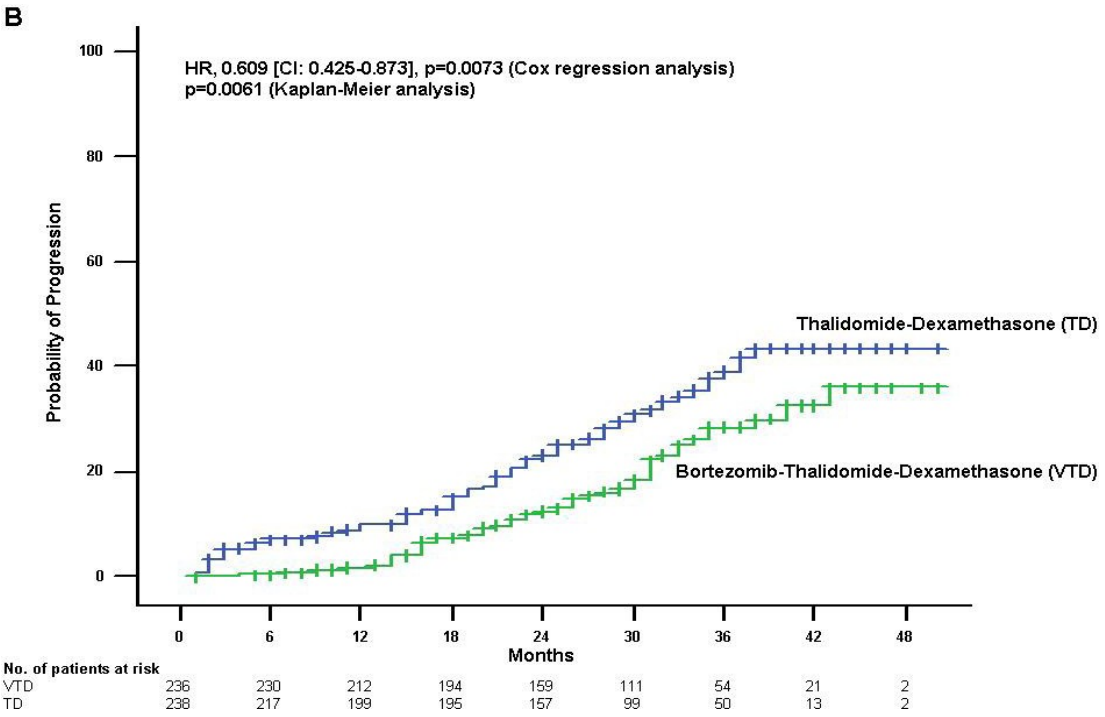


Figure 2: Time to Disease Progression (Study GIMEMA: All Randomised Subjects Analysis Set)



The IFM-2005, Phase III, randomised (1:1:1:1), multi-centre, open-label study was conducted to compare the efficacy and safety of bortezomib-dexamethasone (Vc-Dex) and vincristine-doxorubicin-dexamethasone (VAD) as induction therapy prior to HDT-ASCT, and to evaluate the impact of post-induction consolidation therapy. Patients in this study were randomised to

receive VAD plus no consolidation (arm A1), VAD plus dexamethasone, cyclophosphamide, etoposide, cis-platin (DCEP) consolidation (arm A2), Vc-Dex plus no consolidation (arm B1), or Vc-Dex plus DCEP consolidation (arm B2).

A total of 482 patients aged ≤65 years were randomised; 240 patients received four 3-week cycles of bortezomib (1.3 mg/m^2), days 1, 4, 8 and 11 plus dexamethasone (40 mg) days 1-4 (all cycles) and days 9-12 (cycles 1 and 2), while 242 patients received four 4-week cycles of VAD. The primary endpoint of this study was the CR/nCR rate post-induction.

Patients randomized to the Vc-Dex arm achieved significantly higher rates of complete plus near complete response and very good partial response or better, compared to the VAD arm following induction treatment. Based on an intention to treat analysis, response rates were similar regardless of whether patients received DCEP consolidation or not. Efficacy results are presented in **Table 15**:

Table 15: Response to induction therapy (overall) in the IFM2005 study*

	VAD (A1+A2) N=242	**Vc-Dex (B1+B2) N=240**	***p*-value**
Evaluable population, N	**218**	**223**	
ORR (≥PR), n (%)	137 (62.8)	175 (78.5)	<0.001
≥VGPR	33 (15.1)	84 (37.7)	<0.001
CR/nCR	14 (6.4)	33 (14.8)	0.004
CR	3 (1.4)	13 (5.8)	0.012
MR+SD	58 (26.6)	28 (12.6)	
PD	9 (4.1)	10 (4.5)	
Death	6 (2.8)	1 (0.5)	
Not assessable	8 (3.7)	9 (4.0)	

A total of 184/218 (84.4%) and 197/223 (88.3%) evaluable patients who received VAD and Vc-Dex induction, respectively, underwent autologus stem cell transplantation. The number of patients who received a second transplantation was 41 (20.8%) in the Vc-Dex arm, compared to 50 (27.2%) for patients in the VAD arm. Post-transplant response rates are shown in **Table 16**.

Table 16: Response rates post transplantation*

	VAD (A1+A2) N=242	**Vc-Dex (B1+B2) N=240**	***p*-value**
Response to first transplant			
ORR (≥PR), n (%)	168 (77.1)	179 (80.3)	0.401
≥VGPR	81 (37.2)	121 (54.3)	<0.001
CR/nCR	40 (18.4)	78 (35.0)	<0.001
CR	19 (8.7)	36 (16.1)	0.016
MR+SD+PD	8 (3.7)	6 (2.7)	
Death	2 (0.9)	1 (0.5)	
No transplantation	34 (15.6)	26 (11.7)	
Overall, including second transplantation			
≥VGPR	102 (46.7)	151 (67.7)	<0.001
CR/nCR	49 (22.5)	88 (39.5)	<0.001

* All response assessments were confirmed by an Independent Review Committee.

CR: complete response; MR: minimal response; nCR: near-complete response; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease; VGPR: very good partial response.

In addition, the median PFS was 29.7 months among patients who received VAD versus 36.0 months among patients who received Vc-Dex induction, with 128 (52.9%) of 242 and 110 (45.8%) of 240 patients, respectively, having progressed ($p < .064$, or $p < .057$ if adjusted for initial stratification factors) after median follow-up of 31.2 months.

The efficacy and safety of bortezomib as induction therapy in newly diagnosed multiple myeloma patients were also assessed in various Phase I/II open-label studies. The results from these studies showed that the addition of bortezomib to the various combination chemotherapy regimens resulted in an overall response rates between 66% and 100%.

- Non-Transplant Eligible

The VISTA study is a prospective phase III, international, randomized (1:1), open-label clinical study of 682 patients, conducted to determine whether bortezomib (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarized in **Table 17**.

Table 17: Summary of Baseline Patient and Disease Characteristics in the VISTA Study

Patient Characteristics	**VcMP 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%)
VcMP = bortezomib + melphalan + prednisone; MP = melphalan + prednisone		

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. A statistically significant survival benefit in favour of the VcMP treatment group was observed (HR=0.65; p=0.00084) despite subsequent therapies that included bortezomib based regimens. While the median survival in MP treatment group has now been estimated at 43.1 months, the median survival on the VcMP treatment group has not been reached. Efficacy results are presented in **Table 18** and **Figures 3** and **4**.

Table 18: Summary of Efficacy Analyses in the VISTA study

Efficacy Endpoint	**VcMP 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)	

Efficacy Endpoint	**VcMP n=344**	**MP n=338**
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 Events (deaths) n (%)	45 (13)	76 (23)
Hazard ratio[b] (95% CI)	0.61 (0.42, 0.88)	
p-value [c]	0.00782	
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 (%)	73 (21)	127 (38)
Median[a] (95% CI)	NE (26.1, NE)	20.8 mo (18.3, 28.5)
Hazard ratio[b] (95% CI)	0.52 (0.39, 0.70)	
p-value [c]	0.000009	

[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] 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

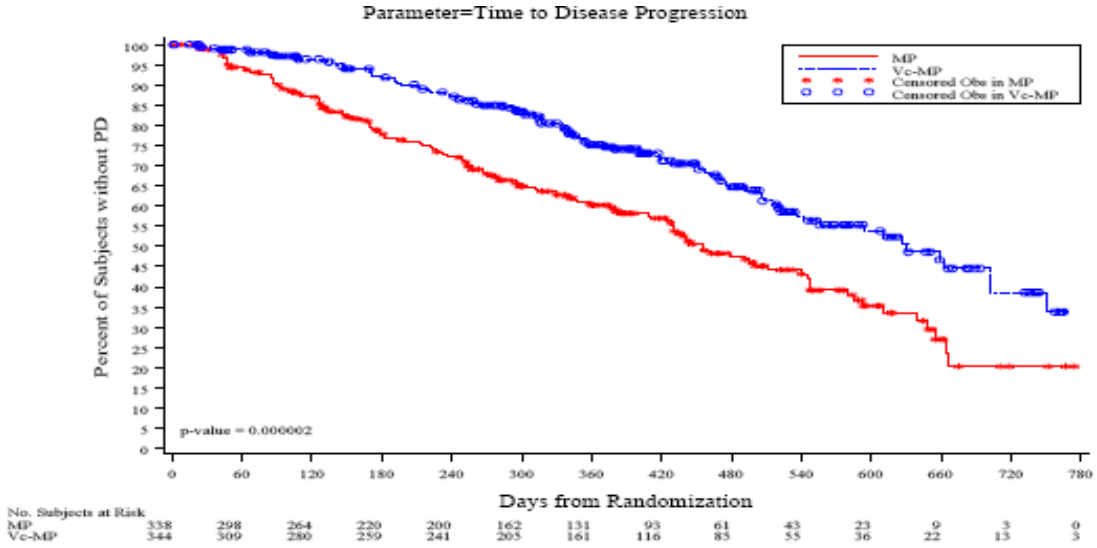
[f] EBMT criteria

[g] All randomized patients with secretory disease

NE: Not estimable

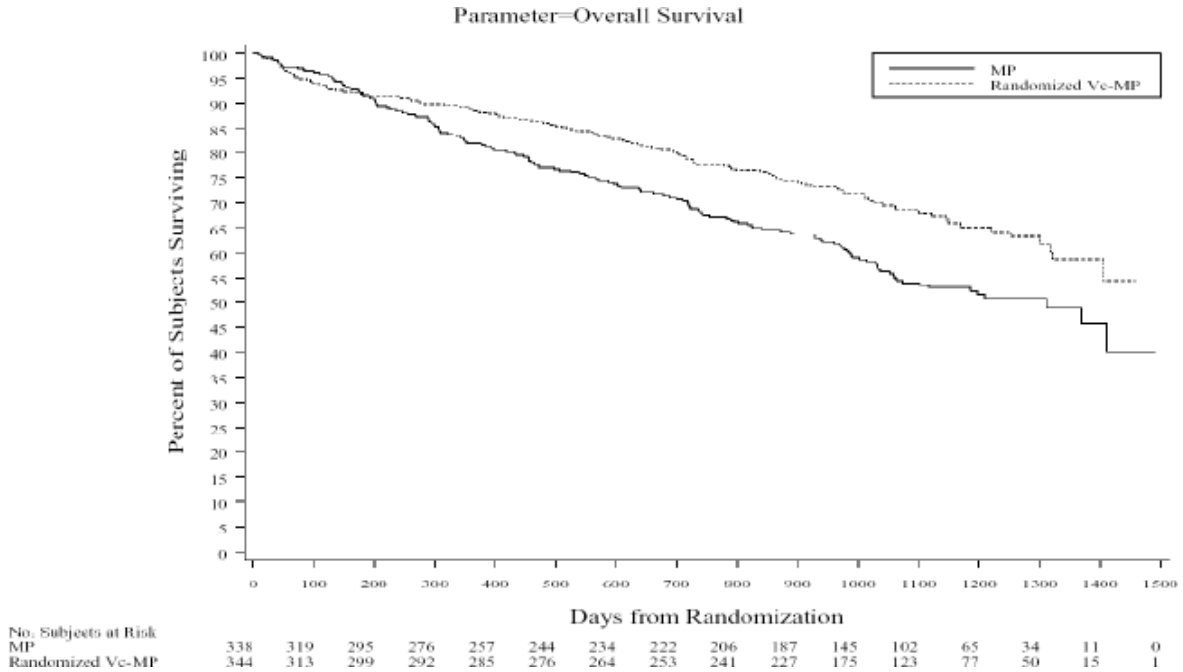
The time to progression (TTP) was significantly longer on the bortezomib arm (see **Figure 3**)

Figure 3: Time to Disease Progression
(Study 26866138-MMY-3002 Update: All Randomised Subjects Analysis Set



A significant survival advantage is shown with bortezomib (see **Figure 4**)

Figure 4: Overall Survival
(Study 26866138-MMY-3002 Update: All Randomised Subjects Analysis Set



Relapsed / Refractory Multiple Myeloma

The safety and efficacy of bortezomib were evaluated in 2 studies at the recommended dose of 1.3 mg/m^2: The APEX study - a phase III randomised, stratified, open-label, comparative study, versus Dexamethasone (Dex), of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy, and a phase II single-arm study of 202 patients with

relapsed and refractory multiple myeloma, who had received at least 2 prior lines of treatment and who were progressing on their most recent treatment (see **Tables 19** and **20**).

Table 19: Dosing regimens in the APEX and Phase II studies

Phase/arm	Drug Schedule	Dose	Regimen
II	bortezomib: Day 1,4,8,11, (rest Day 12-21)	1.3 mg/m^2 (IV bolus)	Q3 weeks x 8 cycles (extension**)
III (APEX)	bortezomib* a) Days 1,4,8,11, (Rest Day 12-21) b) Days 1,8,15,22 (Rest Day 23-35)	1.3 mg/m^2 (IV bolus)	a) Q3 weeks x 8, then b) Q5 weeks x 3
III (APEX)	DEXAMETHASONE Days 1–4, 9–12, 17–20Days 1–4	40 mg (PO)	a) Q5 weeks x 4 b) Q4 weeks x 5
II	Add DEXAMETHASONE***	20 mg (PO) (Days 1,2,4,5,8,9, 11,12)	Q3 weeks

* a) is the initial treatment, a) and b) represent a full course of treatment

** An extension study authorised patients benefiting from treatment to continue receiving bortezomib

*** If after 2 or 4 cycles of bortezomib, the patients had progressive disease or stable disease, respectively, they could receive dexamethasone

Table 20: Patient characteristics in the Phase II* and APEX studies

	Phase II study bortezomib N=202	APEX study bortezomib N=333	APEX study DEX. N=336
Patient characteristics			
Median age in years (range)	59(34-84)	62.0 (33-84)	61.0 (27-86)
Gender: male/female	60% / 40%	56% / 44%	60% / 40%
Karnofsky Performance Status score $\leq$ 70	20%	13%	17%
Haemoglobin <100 g/L	44%	32%	28%
Platelet count <75 x 10^9/L	21%	6%	4%
Disease Characteristics			
Type of myeloma (%): IgG/IgA/Light chain	60%/24%/14%	60%/23%/12%	59%/24%/13%
Median β2-microglobulin (mg/L)	3.5	3.7	3.6
Median creatinine clearance (mL/min)	73.9	73.3	75.3
Abnormal cytogenetics	35%		
Chromosome 13 abnormalities	15%	25.7%	25.0%
Median Duration of Multiple Myeloma Since Diagnosis in Years	**4.0**	**3.5**	**3.1**
Previous Therapy			
Number of Prior Therapeutic Lines of Treatment			
Median (range)**	6 (2-15)	2 (1-7)	2 (1-8)
1 prior line	0	40%	35%
>1 prior line		60%	65%
All patients			
Any prior steroids, e.g., dexamethasone, VAD	99%	98%	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%	91%	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%	77%	76%
Any prior thalidomide therapy	83%	48%	50%
Any prior stem cell transplant/other high-dose therapy	64%	67%	68%
Prior experimental or other types of therapy	44%	3%	2%

*Based on number of patients with baseline data available
**Including steroids, alkylating agents, anthracyclines, thalidomide and stem cell transplants

APEX Study (Phase III)

In the APEX study described above, 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).

Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients randomized to dexamethasone were offered bortezomib, 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. The time to event analyses and response rates from the APEX trial are presented in **Table 21**.

Table 21: Summary of Efficacy Analyses in the APEX Study

	All Patients		**1 Prior Line of Therapy**		**>1 Prior Line of Therapy**	
	bortezomib	**Dex**	**bortezomib**	**Dex**	**bortezomib**	**Dex**
Efficacy Endpoint	**n=333**	**n=336**	**n=132**	**n=119**	**n=200**	**n=217**
Time to Progression – Events n (%)	147(44)	196(58)	55(42)	64(54)	92(46)	132(61)
Median[a] (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 (6.2, 8.8)	5.6 (3.4, 6.3)	4.9 (4.2, 6.3)	2.9 (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 bortezomib.

[c] p-value based on the stratified log-rank test including randomisation 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 dose

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

[g] In 2 patients, the IF was unknown.

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

[i] Not Estimable.

[j] Not Applicable, no patients in category.

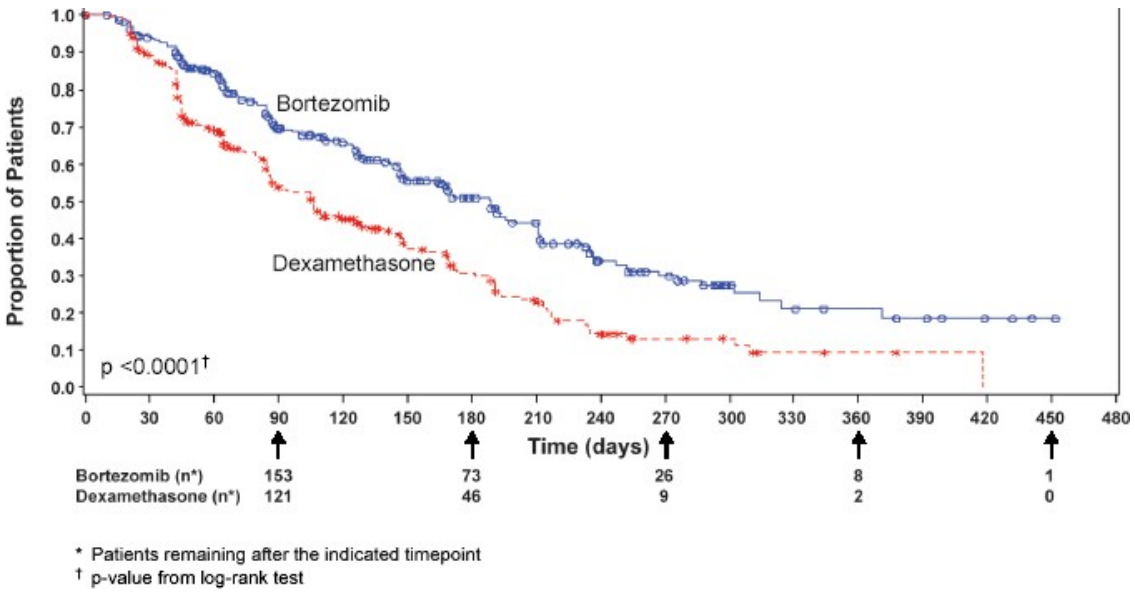
For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the dexamethasone arm.

Treatment with bortezomib led to a significantly longer TTP, a significantly prolonged survival and a significantly higher response rate, compared to treatment with dexamethasone in patients who have received more than one prior therapy as well as in patients who have received only one prior line of therapy.

Both in patients who were refractory to their last prior therapy and those who were not refractory, overall survival was significantly longer and response rate was significantly higher on the bortezomib arm. Of the 669 patients enrolled, 245 (37%) were 65 years of age or older. Response parameters as well as TTP remained significantly better for bortezomib independently of age. Regardless of β2- microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the bortezomib arm.

The time to progression (TTP) was significantly longer on the bortezomib arm (see **Figure 5**).

Figure 5: Time to progression (Bortezomib vs Dexamethasone)

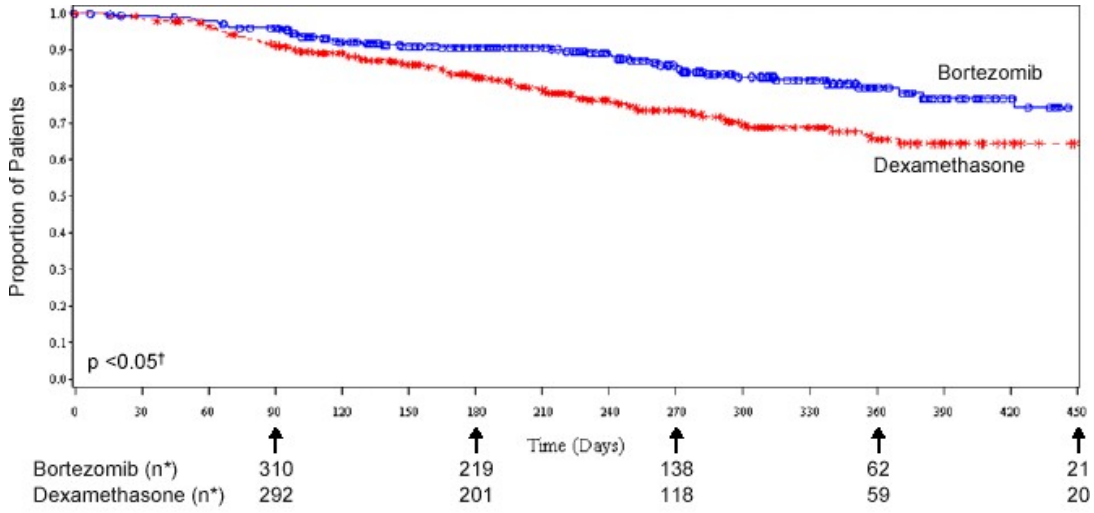


* Patients remaining after the indicated timepoint

† p-value from log-rank test

As shown in **Figure 6**, bortezomib had a significant survival advantage relative to dexamethasone (p<0.05). The median follow-up was 8.3 months.

Figure 6: Overall Survival (Bortezomib vs Dexamethasone)



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

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

An open label, randomized, phase 3 non-inferiority study compared the efficacy and safety of the subcutaneous administration (SC) of bortezomib 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 bortezomib 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 bortezomib alone after 4 cycles were allowed to receive dexamethasone 20 mg daily on the day of and day after bortezomib 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 22**.

Table 22: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial of bortezomib IV vs. SC

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**

Patient Characteristics	IV N=74	SC N=148
Number of Prior Therapeutic Lines of Treatment		
1 prior line	65%	62%
> 1 prior line	35%	38%

This study met its primary objective of non-inferiority for response rate (CR + PR) after 4 cycles of single agent bortezomib for both the SC and IV routes, with an ORR of 42% in both groups. In addition, all secondary endpoints relating to efficacy showed equivalent results between SC and IV administration (**Table 23**).

Table 23: Summary of efficacy analyses for the SC administration of bortezomib compared to IV

	IV bortezomib	SC bortezomib
Response Evaluable Population	**n=73**	**n=145**
Response Rate at 4 cycles		
ORR (CR+PR)	31 (42)	61 (42)
p-value [(a)]	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 [(a)]	0.0001	
CR n (%)	9 (12)	15 (10)
PR n (%)	29(40)	61(42)
nCR n (%)	7(10)	14(10)
Intent to Treat Population [(b)]	**n=74**	**n=148**
TTP, months	**9.4**	**10.4**
(95% CI)	(7.6,10.6)	(8.5,11.7)
Hazard ratio (95% CI) [(c)]	0.839 (0.564,1.249)	
p-value [(d)]	0.38657	
Progression Free Survival, months	8.0	10.2
(95% CI)	(6.7,9.8)	(8.1,10.8)
Hazard ratio (95% CI) [(c)]	0.824 (0.574,1.183)	
p-value [(d)]	0.295	
1-year Overall Survival (%)[(e)]	76.7	72.6
(95% CI)	(64.1,85.4)	(63.1,80.0)

(a) P-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in the IV arm.
(b) 222 subjects were enrolled into the study; 221 subjects were treated with bortezomib
(c) Hazards ratio estimate is based on a Cox model adjusted for stratification factors: ISS staging and number of prior lines.
(d) Log rank test adjusted for stratification factors: ISS staging and number of prior lines.
(e) Median duration of follow up is 11.8 months

Table 24 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 in subsequent cycles (cycle 5 through 8).

- 13% (SC) and 13% (IV) of patients with PR at end of Cycle 4 obtained a CR later in subsequent cycles (cycle 5 through 8).

Table 24: 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 *	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)

*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 bortezomib, APEX, (38% ORR and median TTP of 6.2 months for the bortezomib arm). Time to Progression and ORR was also higher compared to the subgroup of patients on APEX that received only 1 prior line of therapy (43% ORR and median TTP of 7.0 months) (**Table 18**).

Bortezomib 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 bortezomib in 130 patients with relapsed multiple myeloma. Patients had previously tolerated 1.0 or 1.3 mg/m^2 bortezomib alone or in combination with other agents, had CR or PR upon completion of bortezomib therapy, and subsequently relapsed or progressed. Prior to retreatment, at least 6 months should have elapsed since the last dose of bortezomib.

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 including1% 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). The impact of retreatment on survival is unknown.

Currently there are limited data concerning retreatment with bortezomib.

Phase II studies

The safety and efficacy of bortezomib were evaluated in an open-label, single-arm, multi-centre study 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. Dosing regimens and baseline patient and disease characteristics are summarised in **Table 19** and **Table 20**. The study employed dose modifications for toxicity (see **section 4.2**). Responses to bortezomib alone in the phase II study are shown in **Table 25**.

In general, patients who had confirmed Complete Response received 2 additional cycles of bortezomib treatment beyond confirmation. 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). The response rate to bortezomib was independent of the number and types of prior therapies.

Table 25: Summary of disease outcomes in Phase II study

Response Analyses (bortezomib monotherapy) N=188	N (%)	(95% CI)
Overall Response Rate (CR + PR)	52 (27.7%)	(21, 35)
Complete Response (CR)[1]	5 (2.7%)	(1,6)
Partial Response (PR)[2]	47 (25%)	(19, 32)
Clinical Remission (SWOG)[3]	33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	365 Days	(224, NE)

[1]**Complete Response** required 100% disappearance of the original monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.

[2]**Partial Response** required ≥ 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.

[3]**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.

Patients who did not obtain an optimal response to therapy with bortezomib alone were able to receive high-dose dexamethasone in conjunction with bortezomib (i.e., 40 mg dexamethasone with each dose of bortezomib administered orally as 20 mg on the day of and 20 mg the day after bortezomib administration, (i.e., Days 1, 2, 4, 5, 8, 9, 11, and 12), thus 160mg over 3 weeks. Eighteen percent (13/74) of patients achieved or had an improved response (CR 11% or PR 7%) with combination treatment.

A small dose-response study 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 with previously treated light-chain (AL) Amyloidosis

A Phase 1/2 study was conducted to determine the safety and efficacy of bortezomib in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular VECADE 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%.

Paediatric Use

The safety and effectiveness of bortezomib in children has not been established.

5.2 Pharmacokinetic properties

Absorption

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 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib 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 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

In the PK/PD substudy in Phase III 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 (151 ng.h/mL vs 155 ng.h/mL) 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 litres to 3294 litres (489 to 1884L/m^2) following single- or repeat-dose administration of 1.0 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues.

Protein Binding:

Over a bortezomib concentration range of 10 to 1000 ng/mL, the in vitro protein binding averaged 83% in human plasma. The percent of bortezomib bound to plasma proteins was not concentration dependent.

Metabolism:

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, 2D6, 2C9, and 1A2. The major metabolic pathway is deboronation, with the two main metabolites formed undergoing subsequent hydroxylation. One of the two main deboronated metabolites was shown to be inactive as a 26S proteasome inhibitor. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination:

The elimination pathways of bortezomib have not been evaluated in vivo.

Special Populations

Renal Impairment

A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL ≥60 mL/min/1.73 m^2, n=12), Mild (CrCL=40-59 mL/min/1.73 m^2, n=10), Moderate (CrCL=20-39 mL/min/1.73 m^2, n=9), and Severe (CrCL < 20 mL/min/1.73 m^2, n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and Cmax) was comparable among all the groups. (see **section 4.2**)

Hepatic Impairment:

The effect of hepatic impairment (see **Table 6** for definition of hepatic impairment) on the pharmacokinetics of bortezomib was assessed in 51 cancer patients at bortezomib doses ranging 0.5 to 1.3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-randomisation bortezomib AUC. However, the dose-randomalised 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 **sections 4.4** and **4.2 - Table 6**).

5.3 Preclinical safety data

Carcinogenicity studies have not been conducted with bortezomib.

Bortezomib showed clastogenic activity at a high concentration (3 μg/mL) in an *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Clastogenic activity was not observed *in vivo* in a mouse micronucleus test using intravenous doses of up to 3 mg/m^2. Bortezomib was not genotoxic in *in vitro* tests for bacterial gene mutation.

Fertility studies with bortezomib were not performed but degenerative changes seen in the testes and ovary in a rat general toxicity study suggest that bortezomib may affect male and female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol 10mg

Nitrogen

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in **section 6.6**.

6.3 Shelf life

Unopened vial: 3 years

6.4 Special precautions for storage

Unopened vials:

Store below 25°C. Keep the container in the outer carton in order to protect from light.

Reconstituted solution:

BORTEZOMIB JUNO contains no antimicrobial preservative. The chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C when it is stored protected from light in the original vial and/or syringe prior to administration. However, to reduce microbiological hazard, use as soon as possible after dilution and if storage is necessary hold at 2-8°C for up to 8 hours.

6.5 Nature and contents of container

BORTEZOMIB JUNO is supplied in a 5 mL or 10 mL, type I, glass vial with a grey bromobutyl stopper and aluminum seal. The vial is contained in a transparent blister pack consisting of a tray with a lid. The 5 mL vial contains 11 mg powder (1.0 mg bortezomib) for IV injection only and the 10 mL vial contains 38.5 mg powder (3.5 mg bortezomib) for IV or SC injection.

BORTEZOMIB JUNO is available in cartons containing 1 vial. Product is for single use in one patient only.

6.6 Instructions for Use and Handling and Disposal

Administration Precautions:

BORTEZOMIB JUNO 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 BORTEZOMIB JUNO 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 BORTEZOMIB JUNO. BORTEZOMIB JUNO is for IV and subcutaneous use only. **DO NOT ADMINISTER BORTEZOMIB JUNO INTRATHECALLY**.

Reconstitution/Preparation Administration:

Prior to use, the contents of each vial must be reconstituted only with normal (0.9%) saline, Sodium Chloride for Injection 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

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. If any discolouration 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. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Juno Pharmaceuticals NZ Limited

P O Box 76261

Manukau City

Auckland 2241

Email: medical-enquiries@junopharm.com.au

Phone: 0800 816 921

9. DATE OF FIRST APPROVAL

6 April 2020

10. DATE OF REVISION OF THE TEXT

6 April 2020

Summary table of changes

Section changes	Summary of new information