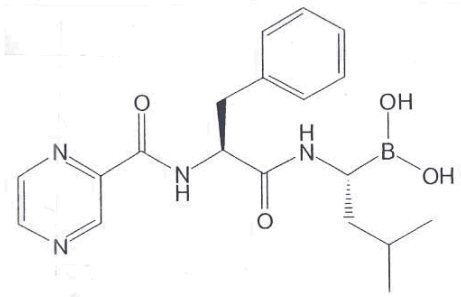
PFIZER BORTEZOMIB POWDER FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Bortezomib

Bortezomib has the following chemical structure:



$C_{19}H_{25}BN_4O_4$ MW: 384.24 CAS Registry No. 179324-69-7

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pfizer Bortezomib Powder for Injection is an antineoplastic agent for intravenous injection (IV) or subcutaneous (SC) use only. Each single dose vial contains

- 3.5 mg of bortezomib as a sterile lyophilised powder.

Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid.

The solubility of bortezomib, as the monomeric boronic acid, in water is: 3.3 – 3.8 mg/mL in a pH range of 2 – 6.5.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pfizer Bortezomib Powder for Injection is indicated as part of combination therapy for the treatment of patients with previously untreated multiple myeloma.

Pfizer Bortezomib Powder for Injection is indicated as monotherapy for the treatment of patients with multiple myeloma who have received at least 1 prior therapy.

Pfizer Bortezomib Powder for Injection is indicated as monotherapy for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Pfizer Bortezomib Powder for Injection in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration

Pfizer Bortezomib Powder for Injection 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)

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

At least 72 hours should elapse between consecutive doses of Pfizer Bortezomib Powder for Injection.

PFIZER BORTEZOMIB POWDER FOR INJECTION IS FOR INTRAVENOUS OR SUBCUTANEOUS USE ONLY. Intrathecal administration has resulted in death.

Recommended Dosage

Previously Untreated Multiple Myeloma - Non-Transplant Eligible

Pfizer Bortezomib Powder for Injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 1. In Cycles 1-4, bortezomib is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, bortezomib is administered once weekly (Days 1, 8, 22 and 29).

Table 1: Recommended Dosage Regimen for Bortezomib when Used in Combination with Melphalan and Prednisone for Patients with Previously Untreated Multiple Myeloma

Twice Weekly Bortezomib (Cycles 1-4)							
Week	**1**			**2**	**3**	**4**	**5**	**6**
Bortezomib (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 (Cycles 5-9)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
Bortezomib (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

m=melphalan, p=prednisone

Dose Management Guidelines

Dose modification and reinitiation of therapy when bortezomib is administered in combination with melphalan and prednisone

Prior to initiating a new cycle of therapy:

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

Table 2: 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 x 10^9/L or ANC ≤0.75 x 10^9/L on a bortezomib dosing day (other than Day 1)	Bortezomib dose should be withheld.
If several bortezomib doses in a cycle are withheld (≥3 doses during twice weekly administration or ≥2 doses during weekly administration)	Bortezomib 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 therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, bortezomib 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-related neuropathic pain and/or peripheral neuropathy, hold and/or modify bortezomib as outlined in Table 3.

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

Table 3: Recommended Dose Modification for Bortezomib-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 to 1.0 mg/m^2 OR Change bortezomib 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 therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib.

* Grading based on NCI Common Toxicity Criteria CTCAE v 4.0.
** Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.
*** Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Relapsed/Refractory Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Recommended Dose

The recommended dose of bortezomib 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.

It is recommended that patients with a confirmed complete response receive 2 additional cycles of bortezomib 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 therapy.

For extended therapy of more than 8 cycles, bortezomib may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) (see section 5.1 for a summary of dose administration during clinical trials).

Dose Modification and Reinitiation of Therapy

Bortezomib therapy should be withheld at the onset of any Grade 3 non-haematological or Grade 4 haematological toxicities excluding neuropathy as discussed above (see section 4.4). Once the symptoms of the toxicity have resolved, bortezomib 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 3 contains the recommended dose modification for the management of patients who experience bortezomib-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 only after careful risk/benefit assessment.

Previously Untreated Mantle Cell Lymphoma

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

Pfizer Bortezomib Powder for Injection is administered at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on Days 1, 4, 8, and 11, followed by a 10-day rest period on Days 12-21. This 3-week period is considered a treatment cycle. Six bortezomib cycles are recommended, although for patients with a response first documented at Cycle 6, two additional bortezomib cycles may be given. At least 72 hours should elapse between consecutive doses of bortezomib.

The following medicinal products are administered on Day 1 of each bortezomib 3-week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2, and doxorubicin at 50 mg/m^2.

Prednisone is administered orally at 100 mg/m^2 on Days 1, 2, 3, 4 and 5 of each treatment cycle.

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

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥100 x 10^9/L and ANC should be ≥1.5 x 10^9/L
- Haemoglobin should be ≥8 g/dL
- Non-haematologic toxicity should have recovered to Grade 1 or baseline

Bortezomib treatment must be withheld at the onset of any ≥Grade 3 bortezomib-related non-haematological toxicities (excluding neuropathy) or ≥Grade 3 haematological toxicities (see also section 4.4). For dose adjustments, see Table 4 below. Colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Platelet transfusion for the treatment of thrombocytopenia may be considered.

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

Toxicity	**Posology modification or delay**
Haematological toxicity • ≥Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count <10 x 10^9/L	Bortezomib therapy should be withheld for up to 2 weeks until the patient has an ANC ≥0.75 x 10^9/L and a platelet count ≥25 x 10^9/L. • If, after bortezomib has been held, the toxicity does not resolve, as defined above, then bortezomib must be discontinued.

	• If toxicity resolves i.e., patient has an ANC ≥0.75 x 10^9/L and a platelet count ≥25 x 10^9/L, bortezomib may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
• If platelet counts <25 x 10^9/L. or ANC <0.75 x 10^9/L on a bortezomib dosing day (other than Day 1 of each cycle)	Bortezomib dose should be withheld.
Grade ≥3 non-haematological toxicities considered to be related to bortezomib	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, bortezomib 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-related neuropathic pain and/or peripheral neuropathy, hold and/or modify bortezomib as outlined in Table 3.

In addition, when bortezomib is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective Product Information documents.

Patients with Renal Impairment

Based on the data from a small study, the pharmacokinetics of bortezomib are not influenced by mild (CrCL=40-59 mL/min/1.73 m^2, n=10) or moderate (CrCL=20-39 mL/min/1.73 m^2, n=9) renal impairment. Therefore, dosing adjustments of bortezomib are not necessary for these patients. The effect of severe renal impairment (CrCL<20 mL/min/1.73 m^2) has not been determined. Since dialysis may reduce bortezomib 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 dose. Patients with moderate or severe hepatic impairment should be started on bortezomib 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 5).

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

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	≤1.0 x ULN	>ULN	None
	>1.0 x - 1.5 x ULN	Any	None
Moderate	>1.5 x - 3 x ULN	Any	

Severe	>3 x ULN	Any	Reduce bortezomib to 0.7 mg/m^2 in the first cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.

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

Paediatric Use

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

Method of Administration

Intravenous injection (IV)

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

When bortezomib is given in combination with other medicinal products, refer to the Product Information for these products for instructions for administration.

4.3 Contraindications

Pfizer Bortezomib Powder for Injection is contraindicated in patients with acute diffuse infiltrative pulmonary and pericardial disease and 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.

Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of bortezomib. Bortezomib is for intravenous or subcutaneous 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.

Gastrointestinal toxicity

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.

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with bortezomib (see section 4.8).

Multiple Myeloma

Antiviral prophylaxis was administered to 26% of the patients in the Bortezomib-+M+P arm. The incidence of herpes zoster among patients in the Bortezomib+M+P treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Mantle Cell Lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the BR-CAP arm. The incidence of herpes zoster among patients in the BR-CAP arm was 4.6% for patients not administered antiviral prophylaxis compared to 0.8% for patients administered antiviral prophylaxis.

Hepatitis B virus (HBV) reactivation and infection

When rituximab is used in combination with bortezomib, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with bortezomib. Antiviral prophylaxis should be considered. Refer to the local Product Information of rituximab for more information.

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 3 multiple myeloma 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 2 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.

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

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.

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 2 and 3 studies, the incidence of hypotension (postural, orthostatic and hypotension not otherwise specified) was 11% to 12%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope 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).

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.

Heart failure

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 3 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 oedema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary oedema) 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 aetiology 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 (2 g/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. Therefore, this specific regimen with concomitant administration with high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

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

Renal impairment

The incidence of serious undesirable effects may increase in patients with renal impairment compared to patients with normal renal function. Renal complications are frequent in patients with multiple myeloma. Such patients should be monitored closely. The safety of bortezomib in patients with severe renal impairment (CrCL<20 mL/min/1.73 m^2) has not been established. The effect of dialysis on bortezomib plasma concentrations has also not been determined. However, since dialysis may reduce bortezomib concentrations, the drug should be administered after the dialysis procedure.

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. The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in 60 cancer patients with

varying degrees of hepatic impairment treated bortezomib doses ranging from 0.5 to 1.3 mg/m^2 (see Table 5 for definition of hepatic impairment). When compared to patients with normal hepatic function, mild hepatic impairment did not alter bortezomib dose-normalised AUC. However, the dose-normalised mean AUC values were increased by approximately 60% in patients with moderate to severe hepatic impairment.

Hepatic reactions

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, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib. There is limited re-challenge information in these patients.

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.

Amyloidosis

A Phase 1/2 single-agent bortezomib dose-escalation study was conducted in patients with previously treated light-chain amyloidosis. At planned interim analysis, no new safety concerns were observed and no evidence of target organ damage was found during the study.

Laboratory tests

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

Thrombocytopenia/Neutropenia

Bortezomib treatment is associated with thrombocytopenia and neutropenia (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. The pattern of platelet count decrease and recovery remained consistent, in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied.

Platelet counts should be monitored prior to each dose of bortezomib. Bortezomib therapy should be held when the platelet count is <25,000/μL (see sections 4.2 and 4.8). There have been reports of gastrointestinal and intracerebral haemorrhage in association with bortezomib. Transfusion and supportive care may be considered at the discretion of the physician.

In the single-agent multiple myeloma study of bortezomib vs dexamethasone, 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 6 for the Phase 3 study. The incidence of significant bleeding events (≥Grade 3) was similar on both the bortezomib (4%) and dexamethasone (5%) arms.

Table 6: The Severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the APEX Study of Bortezomib IV vs. Dexamethasone

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 – 25,000 µL
≥75,000/µL	309	8 (3%)	36 (12%)
≥50,000/µL - <75,000/µL	14	2 (14%)	11 (79%)
≥10,000/µL - <50,000/µL	7	1(14%)	5 (71%)

*A baseline platelet count of 50,000/µL was required for study eligibility.
** Data for one patient was missing at baseline.
Thrombocytopenia was reported in 43% of patients in the Phase 2 studies.

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

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

The incidence of neutropenia (≥Grade 4) was 70% in the BR-CAP arm and was 52% in the R-CHOP arm. The incidence of febrile neutropenia (≥Grade 4) was 5% in the BR-CAP arm and was 6% in the R-CHOP arm. Colony-stimulating factor support was provided at a rate of 78% in the BR-CAP arm and 61% in the R-CHOP arm.

Use in mantle cell lymphoma (MCL) patients eligible for autologous stem cell transplantation

The pivotal study in previously untreated MCL patients mainly studied patients ineligible for autologous stem cell transplantation, and evidence of efficacy and safety in patients eligible for transplantation is more limited. In particular, there are no data directly informing about the use of BR-CAP as an induction regimen in previously untreated MCL patients who have subsequently received a transplant.

Potentially immunocomplex-mediated reactions

Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. Bortezomib should be discontinued if serious reactions occur.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro and animal *ex vivo* studies indicate that bortezomib is a weak inhibitor of cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6, and 3A4. Bortezomib did not induce the activities

of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metaboliser phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole (a potent CYP3A4 inhibitor) on the pharmacokinetics of 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 CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort. In the same drug-drug interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.

Patients who are concomitantly receiving bortezomib and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy.

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, antivirals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

4.6 Fertility, pregnancy and lactation

Contraception in Males and Females

Due to the genotoxic potential of bortezomib (see section 5.3), women of childbearing potential must use effective contraceptive measures and avoid becoming pregnant while being treated with bortezomib and for 8 months following completion of treatment. Male patients should use effective contraceptive measures and be advised not to father a child while receiving bortezomib and for 5 months following completion of treatment (see section 5.3).

Pregnancy

Women of childbearing 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 foetus, 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.

Breast-feeding

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.

Fertility

Fertility studies with bortezomib were not performed. Due to the genotoxic potential of bortezomib (see section 5.3), male patients should seek advice on conservation of sperm and women of childbearing potential should seek consultation regarding oocyte cryopreservation prior to initiation of treatment.

4.7 Effects 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

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

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

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

	Study No.	
MedDRA System Organ Class Preferred Term	039 (N=331)	024/025 (N=228[a])
Blood and lymphatic system disorders		
Thrombocytopenia	115 (35%)	97 (43%)
Anaemia	87 (26%)	74 (32%)
Neutropenia	62 (19%)	55 (24%)
Leucopenia	24 (7%)	15 (7%)
Lymphopenia	15 (5%)	11 (5%)
Pancytopenia	2 (<1%)	6 (3%)
Febrile neutropenia	1 (<1%)	1 (<1%)
Cardiac disorders		
Arrhythmias	4 (1%)	2 (<1%)
Tachycardia	9 (3%)	17 (7%)
Atrial fibrillation	6 (2%)	2 (<1%)
Palpitations	5 (2%)	4 (2%)
Acute development or exacerbation of cardiac failure, including CHF	7 (2%)	8 (4%)
Pulmonary oedema	6 (2%)	3 (1%)
Cardiogenic shock[b]	1 (<1%)	-
New onset of decreased left ventricular ejection fraction	1 (<1%)	-
Atrial flutter	1 (<1%)	-
Bradycardia	3 (<1%)	1 (<1%)
Ear and labyrinth disorders		
Hearing impairment	1 (<1%)	1 (<1%)
Eye disorders		
Blurred vision	9 (3%)	25 (11%)
Conjunctival infection and irritation	14 (4%)	7 (3%)
Gastrointestinal (GI) disorders		
Constipation	140 (42%)	97 (43%)
Diarrhoea	190 (57%)	116 (51%)
Nausea	190 (57%)	145 (64%)
Vomiting	117 (35%)	82 (36%)
Gastrointestinal and abdominal pain, excluding oral and throat	80 (24%)	48 (21%)
Dyspepsia	32 (10%)	30 (13%)
Pharyngolaryngeal pain	25 (8%)	19 (8%)
Gastroesophageal reflux	10 (3%)	1 (<1%)
Eructation	2 (<1%)	4 (2%)
Abdominal distension	14 (4%)	13 (6%)
Stomatitis and mouth ulceration	24 (7%)	10 (4%)
Dysphagia	4 (1%)	5 (2%)
GI haemorrhage (upper and lower GI tract)[b]	7 (2%)	3 (1%)
Rectal haemorrhage (includes haemorrhagic diarrhoea)	7 (2%)	3 (1%)
Tongue ulceration	2 (<1%)	1 (<1%)

	Study No.	
MedDRA System Organ Class Preferred Term	039 (N=331)	024/025 (N=228[a])
Retching	3 (<1%)	2 (<1%)
Upper GI haemorrhage	1 (<1%)	-
Haematemesis	1 (<1%)	-
Oral mucosal petechiae	3 (<1%)	-
Ileus paralytic	1 (<1%)	2 (<1%)
General disorders and administration site conditions		
Asthenic conditions	201 (61%)	149 (65%)
weakness	40 (12%)	44 (19%
fatigue	140 (42%)	118 (52%)
lethargy	12 (4%)	9 (4%)
malaise	13 (4%)	22 (10%)
Pyrexia	116 (35%)	82 (36%)
Rigors	37 (11%)	27 (12%)
Oedema of the lower limbs	35 (11%)	27 (12%)
Neuralgia	21 (6%)	5 (2%)
Chest pain	26 (8%)	16 (7%)
Injection site pain and irritation	1 (<1%)	1 (<1%)
Injection site phlebitis	1 (<1%)	1 (<1%)
Hepatobiliary disorders		
Hyperbilirubinaemia	1 (<1%)	-
Abnormal liver function tests	3 (<1%)	2 (<1%)
Hepatitis	2 (<1%) in study M34101-040[c]	-
Immune system disorders		
Drug hypersensitivity	1 (<1%)	1 (<1%)
Infections and infestations		
Upper respiratory tract infection	26 (8%)	41 (18%)
Nasopharyngitis	45 (14%)	17 (7%)
Lower respiratory tract and lung infections	48 (15%)	29 (13%)
Pneumonia[b]	21 (6%)	23 (10%)
Herpes zoster (including multidermatomal or disseminated)	42 (13%)	26 (11%)
Herpes simplex	25 (8%)	13 (6%)
Bronchitis	26 (8%)	6 (3%)
Postherpetic neuralgia	4 (1%)	1 (<1%)
Sinusitis	14 (4%)	15 (7%)
Pharyngitis	6 (2%)	2 (<1%)
Oral candidiasis	6 (2%)	3 (1%)
Urinary tract infection	13 (4%)	14 (6%)
Catheter related infection	10 (3%)	6 (3%)
Sepsis and bacteraemia[b]	9 (3%)	9 (4%)
Gastroenteritis	7 (2%)	-
Injury, poisoning, and procedural complications		
Catheter related complication	7 (2%)	8 (4%)
Investigations		

	Study No.	
MedDRA System Organ Class Preferred Term	039 (N=331)	024/025 (N=228[a])
Increased ALT	3 (<1%)	10 (4%)
Increased AST	5 (2%)	12 (5%)
Increased alkaline phosphatase	6 (2%)	8 (4%)
Increased GGT	1 (<1%)	4 (2%)
Metabolism and nutritional disorders		
Decreased appetite and anorexia	112 (34%)	99 (43%)
Dehydration	24 (7%)	42 (18%)
Hyperglycaemia	5 (2%)	16 (7%)
Hypoglycaemia	7 (2%)	4 (2%)
Hyponatraemia	8 (2%)	18 (8%)
Tumour lysis syndrome	2 (<1%) in study M34101-040[c]	-
Musculoskeletal and connective tissue disorders		
Pain in limb	50 (15%)	59 (26%)
Myalgia	39 (12%)	32 (14%)
Arthralgia	45 (14%)	60 (26%)
Nervous system disorders		
Peripheral neuropathy[d]	120 (36%)	84 (37%)
Paraesthesia and dysaesthesia	91 (27%)	53 (23%)
Dizziness, excluding vertigo	45 (14%)	48 (21%)
Headache	85 (26%)	63 (28%)
Dysgeusia	17 (5%)	29 (13%)
Polyneuropathy	9 (3%)	1 (<1%)
Syncope	8 (2%)	17 (7%)
Convulsions	4 (1%)	-
Loss of consciousness	2 (<1%)	-
Ageusia	2 (<1%)	-
Psychiatric disorders		
Anxiety	31 (9%)	32 (14%)
Renal and urinary disorders		
Renal impairment and failure	21 (6%)	21 (9%)
Difficulty in micturition	2 (1%)	3 (1%)
Haematuria	5 (2%)	4 (2%)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	21 (6%)	23 (10%)
Cough	70 (21%)	39 (17%)
Dyspnoea	65 (20%)	50 (22%)
Exertional dyspnoea	21 (6%)	18 (8%)
Pleural effusion	4 (1%)	9 (4%)
Rhinorrhoea	4 (1%)	14 (6%)
Haemoptysis	3 (<1%)	2 (<1%)
Skin and subcutaneous tissue disorders		
Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vasculitis	61 (18%)	47 (21%)
Urticaria	7 (2%)	5 (2%)

	Study No.	
MedDRA System Organ Class Preferred Term	039 (N=331)	024/025 (N=228[a])
Vascular disorders		
Hypotension	20 (6%)	27 (12%)
Orthostatic/postural hypotension	14 (4%)	8 (4%)
Petechiae	6 (2%)	7 (3%)
Cerebral haemorrhage[b]	1 (<1%)	-

[a] All 228 patients received Bortezomib at a dose of 1.3 mg/m^2.
[b] Includes fatal outcome.
[c] A study of Bortezomib at the recommended dose of 1.3 mg/m^2 in multiple myeloma patients who experienced progressive disease after receiving at least four previous therapies or after receiving high-dose dexamethasone in Protocol M34101-039.
[d] Including all preferred terms under the MedDRA HLT "peripheral neuropathy NEC".

Serious Adverse Events (SAEs) and Events Leading to Treatment Discontinuation in the Phase 3 Multiple Myeloma Study

Serious adverse events are defined as any event, regardless of causality, that results in death, is life-threatening, requires hospitalisation or prolongs a current hospitalisation, results in a significant disability, or is deemed to be an important medical event. A total of 144 (44%) patients from the Bortezomib treatment arm experienced an SAE during the study. The most commonly reported SAEs in the Bortezomib treatment arm were pyrexia (6%), diarrhoea (5%), dyspnoea and pneumonia (4%), and vomiting (3%). 84 (25%) of 331 patients in the Bortezomib treatment group were discontinued from treatment due to adverse events assessed as drug-related by the investigators. Among the 331 Bortezomib treated patients, the most commonly reported drug-related event leading to discontinuation was peripheral neuropathy (8%). Four deaths were considered to be Bortezomib related in the phase 3 multiple myeloma study: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest.

Non-randomised Phase 2 Clinical Studies

Serious Adverse Events (SAEs)

A total of 113 (50%) of 228 patients in the Phase 2 studies experienced SAEs during the studies. The most commonly reported SAEs included pyrexia and pneumonia (each 7%), diarrhoea (6%), vomiting and dehydration (each 5%) and nausea (4%).

In Phase 2 clinical studies, adverse events thought by the investigator to be drug-related and leading to discontinuation occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy (5%), thrombocytopenia (4%), and diarrhoea and fatigue (each 2%).

Two deaths were reported and considered by the investigator to be possibly related to study drug: 1 case pulmonary arrest and 1 case of respiratory failure.

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 3 study at the recommended dose of 1.3 mg/m^2. This was a randomised, comparative study of Bortezomib IV vs SC in 222 patients with relapsed multiple myeloma.

Table 8: 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 9: 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[a]	39 (53)	12 (16)	10 (14)	56 (38)	9 (6)	9 (6)

[a] Represents the high level term.
TEAE=Treatment-Emergent Adverse Event; G ≥3 = Toxicity Grade greater than or equal to 3.
Disc=Discontinuation of any study drug.

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

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

Summary of Clinical Trials in Patients with Previously Untreated Multiple Myeloma

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

Table 10: Treatment-Emergent Drug-Related Adverse Events Reported in ≥10% of Patients Treated with Bortezomib IV in Combination with Melphalan and Prednisone

	B+M+P (n=340)			M+P (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)
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 Phase 3 study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with B+M+P compared with M+P (14% vs 4% respectively). Antiviral prophylaxis was

administered to 26% of the patients in the B+M+P arm. The incidence of herpes zoster among patients in the B+M+P treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Summary of Clinical Trial in Patients with Relapsed Mantle Cell Lymphoma

Safety data for patients with relapsed mantle cell lymphoma were evaluated in a Phase 2 study [M34103-053 (PINNACLE)], which included 155 patients treated with Bortezomib at the recommended dose of 1.3 mg/m^2. The safety profile of Bortezomib in these patients was similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, anaemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and pruritus were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.

Summary of Clinical Trial in Patients with Previously Untreated Mantle Cell

Lymphoma

Table 11 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received Bortezomib (1.3 mg/m^2) administered IV in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (BR-CAP) in a prospective randomised study.

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

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

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

Table 11: Most Commonly Reported Adverse Reactions (≥5%) with Grades 3 and ≥4 Intensity in the Mantle Cell Lymphoma Study of BR-CAP versus R-CHOP (N=482) (Study LYM-3002)

	BR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Blood and lymphatic system disorders						
Neutropenia	209 (87)	32 (13)	168 (70)	172 (71)	31 (13)	125 (52)
Leukopenia	116 (48)	34 (14)	69 (29)	87 (36)	39 (16)	27 (11)
Anaemia	106 (44)	27 (11)	4 (2)	71 (29)	23 (10)	4 (2)
Thrombocytopenia	172 (72)	59 (25)	76 (32)	42 (17)	9 (4)	3 (1)
Febrile neutropenia	41 (17)	24 (10)	12 (5)	33 (14)	17 (7)	15 (6)
Lymphopenia	68 (28)	25 (10)	36 (15)	28 (12)	15 (6)	2 (1)

	BR-CAP n=240			R-CHOP n=242		
System Organ Class Preferred Term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Nervous system disorders						
Peripheral sensory neuropathy	53 (22)	11 (5)	1 (<1)	45 (19)	6 (3)	0
Neuropathy peripheral	18 (8)	4 (2)	0	18 (7)	2 (1)	0
Hypoaesthesia	14 (6)	3 (1)	0	13 (5)	0	0
Paraesthesia	14 (6)	2 (1)	0	11 (5)	0	0
Neuralgia	25 (10)	9 (4)	0	1 (<1)	0	0
General disorders and administration site conditions						
Fatigue	43 (18)	11 (5)	1 (<1)	38 (16)	5 (2)	0
Pyrexia	48 (20)	7 (3)	0	23 (10)	5 (2)	0
Asthenia	29 (12)	4 (2)	1 (<1)	18 (7)	1 (<1)	0
Oedema peripheral	16 (7)	1 (<1)	0	13 (5)	0	0
Gastrointestinal disorders						
Nausea	54 (23)	1 (<1)	0	28 (12)	0	0
Constipation	42 (18)	1 (<1)	0	22 (9)	2 (1)	0
Stomatitis	20 (8)	2 (1)	0	19 (8)	0	1 (<1)
Diarrhoea	59 (25)	11 (5)	0	11 (5)	3 (1)	1 (<1)
Vomiting	24 (10)	1 (<1)	0	8 (3)	0	0
Abdominal distension	13 (5)	0	0	4 (2)	0	0
Infections and infestations						
Pneumonia	20 (8)	8 (3)	5 (2)	11 (5)	5 (2)	3 (1)
Skin and subcutaneous tissue disorders						
Alopecia	31 (13)	1 (<1)	1 (<1)	33 (14)	4 (2)	0
Metabolism and nutrition disorders						
Hyperglycaemia	10 (4)	1 (<1)	0	17 (7)	10 (4)	0
Decreased appetite	36 (15)	2 (1)	0	15 (6)	1 (<1)	0
Hypokalaemia	11 (5)	3 (1)	1 (<1)	6 (2)	1 (<1)	0
Vascular disorders						
Hypertension	15 (6)	1 (<1)	0	3 (1)	0	0
Psychiatric disorders						
Insomnia	16 (7)	1 (<1)	0	8 (3)	0	0

Key: R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
BR-CAP=Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Post-Marketing Experience

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

The frequencies provided below reflect reporting rates of adverse drug reactions from the worldwide post-marketing experience with Bortezomib. The frequencies provided below reflect reporting rates and precise estimates of incidence cannot be made.

These adverse drug reactions are ranked by frequency, using the following convention: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000, including isolated reports).

Table 12: Post-marketing Reports of Adverse Reactions

Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Thrombotic microangiopathy	Very rare
Cardiac disorders	
Atrioventricular block complete, cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye disorders	
Ophthalmic herpes, optic neuropathy, blindness	Rare
Chalazion/blepharitis	Rare
Gastrointestinal disorders	
Ischaemic colitis, acute pancreatitis	Rare
Intestinal obstruction	Uncommon
Infections and infestations	
Herpes meningoencephalitis, septic shock	Rare
Progressive multifocal leukoencephalopathy[a]	Very rare
Immune system disorders	
Angioedema	Rare
Anaphylactic reaction	Very rare
Nervous system disorders	
Encephalopathy, autonomic neuropathy, posterior reversible encephalopathy syndrome, Guillain-Barré syndrome, demyelinating polyneuropathy	Rare
Respiratory, thoracic and mediastinal disorders	
Acute diffuse infiltrative pulmonary disease (see section 4.4)	Rare
Pulmonary hypertension	Rare
Skin and subcutaneous tissue disorders	
Stevens-Johnson Syndrome and toxic epidermal necrolysis	Very rare
Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Rare

[a] Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with 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 activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

Clinical Trials

Phase 2 Clinical Studies in Relapsed Multiple Myeloma

The safety and efficacy of Bortezomib IV in relapsed multiple myeloma were evaluated in an open-label, single-arm, multicentre 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 6. Baseline patient and disease characteristics are summarised in Table 13.

An IV bolus injection of Bortezomib 1.3 mg/m^2/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 8 treatment cycles. The study employed dose modifications for toxicity (see section 4.2). Patients who experienced a response to Bortezomib were allowed to continue Bortezomib treatment in an extension study.

Table 13: Summary of Patient Population and Disease Characteristics in a Phase 2 Multiple Myeloma Study[a]

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

Median β_2-microglobulin (mg/L)	3.5
Median creatinine clearance (mL/min)	73.9
Abnormal cytogenetics	35%
Chromosome 13 deletion	15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any prior steroids, e.g., dexamethasone, VAD	99%
Any prior alkylating agents, e.g., MP, VBMCP	92%
Any prior anthracyclines, e.g., VAD, mitoxantrone	81%
Any prior thalidomide therapy	83%
Received at least 2 of the above	98%
Received at least 3 of the above	92%
Received all 4 of the above	66%
Any prior stem cell transplant/other high-dose therapy	64%
Prior experimental or other types of therapy	44%

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

Responses to Bortezomib alone are shown in Table 14. Response rates to Bortezomib alone were determined by an independent review committee (IRC) based on criteria published by Bladé and others. Complete response required <5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-). Response rates using the Southwest Oncology Group (SWOG) criteria are also shown. SWOG response required a ≥75% reduction in serum myeloma protein and/or ≥90% urine protein. A total of 188 patients were evaluable for response; 9 patients with non-measurable disease could not be evaluated for response by the IRC, and 5 patients were excluded from the efficacy analyses because they had minimal prior therapy.

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

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

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

Table 14: Summary of Disease Outcomes in a Phase 2 Multiple Myeloma Study

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

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

[b] Partial Response requires ≥50% reduction in serum myeloma protein and ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

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

Of the 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%) of patients aged 65 years or older experienced CR or PR.

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

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

Patients who did not obtain an optimal response to therapy with Bortezomib alone (progressive or stable disease after 2 or 4 cycles, respectively) 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 160 mg over 3 weeks). A total of 74 patients were administered dexamethasone in combination with Bortezomib and were assessed for response. Eighteen percent (13/74) of patients achieved or had an improved response (CR 11% or PR 7%) with combination treatment.

Randomised, Open-Label, Phase 3 Clinical Study in Relapsed Multiple Myeloma comparing Bortezomib to Dexamethasone

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

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

Baseline patient and disease characteristics are summarised in Table 15.

Table 15: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial

Patient Characteristics	Bortezomib N=333	Dexamethasone N=336
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: Male/female	56% / 44%	60% / 40%
Race: Caucasian/Black/other	90% / 6% / 4%	88% / 7% / 5%

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

Patients in the Bortezomib treatment group were to receive eight 3-week treatment cycles followed by three 5-week treatment cycles of Bortezomib. Within each 3-week treatment cycle, Bortezomib 1.3 mg/m^2/dose alone was administered by IV bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). Within each 5-week treatment cycle, Bortezomib 1.3 mg/m^2/dose alone was administered by IV bolus once weekly for 4 weeks on Days 1, 8, 15, and 22 followed by a 13-day rest period (Days 23 to 35) (see section 4.2).

Patients in the dexamethasone treatment group were to receive four 5-week treatment cycles followed by five 4-week treatment cycles. Within each 5-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a 15-day rest period (Days 21-35). Within each 4-week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24-day rest period (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered Bortezomib at a standard dose and schedule on a companion study.

Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients randomised 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.

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

The time to event analyses and response rates from the Phase 3 multiple myeloma study are presented in Table 16. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Complete response (CR) required <5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-). Partial Response (PR) requires ≥50% reduction in serum myeloma protein and ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis, however M-protein was still detectable by immunofixation (IF^+).

Table 16: Summary of Efficacy Analyses in the Phase 3 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 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio[b] (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value[c]	<0.0001		0.0019		<0.0001	
Overall Survival						
Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio[b] (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value[c,d]	<0.05		<0.05		<0.05	
Response Rate						
Population[e] n=627	n=315	n=312	n=128	n=110	n=187	n=202
CR[f] n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR[f] n (%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR[f,g] n (%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR[f] n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value[h]	<0.0001		0.0035		<0.0001	
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 drug.

[f] EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria. nCR is in the PR category.
[g] In 2 patients, the IF was unknown.
[h] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors.
[i] Not Estimable.
[j] Not Applicable, no patients in category.

Randomised, Open-Label Clinical Study in Relapsed Multiple Myeloma Comparing Bortezomib IV and SC

An open-label, randomised, 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 randomised 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 after Bortezomib administration. Patients with baseline Grade ≥2 peripheral neuropathy or platelet counts <50000/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 beta2-microglobulin and albumin levels; Stages I, II, or III).

Baseline patient and disease characteristics are summarised in Table 17.

Table 17: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial of Bortezomib IV vs SC

Patient Characteristics	**IV**	**SC**
	N=74	**N=148**
Median age in years (range)	64.5 (38,86)	64.5 (42,88)
Gender: male/female	64% / 36%	50% / 50%
Race: Caucasian/Asian	96% / 4%	97% / 3%
Karnofsky performance status score ≤70	16%	22%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	72% / 19% / 8%	65% / 26% / 8%
ISS staging[a] I/II/III (%)	27 / 41 / 32	27 / 41 / 32
Median β_2-microglobulin (mg/l)	4.25	4.20
Median albumin (g/l)	3.60	3.55
Creatinine clearance ≤30 ml/min [n (%)]	2 (3%)	5 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	2.93	2.68
Number of Prior Therapeutic Lines of Treatment		
1 prior line	65%	62%
>1 prior line	35%	38%

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

This study met its primary objective of non-inferiority for response rate (CR + PR) after 4 cycles of single agent Bortezomib for both the SC and IV routes, 42% in both groups. In

addition, secondary response-related and time to event related efficacy endpoints showed consistent results for SC and IV administration (Table 18).

Table 18: Summary of Efficacy Analyses for the SC Administration of Bortezomib Compared to IV

	IV Bortezomib	SC Bortezomib
Response-Evaluable Population[a]	**N=73**	**N=145**
Response Rate at 4 cycles		
ORR (CR+PR)	31 (42)	61 (42)
p-value[b]	0.00201	
CR n (%)	6 (8)	9 (6)
PR n (%)	25 (34)	52 (36)
nCR n (%)	4 (5)	9 (6)
Response Rate at 8 cycles		
ORR (CR+PR)	38 (52)	76 (52)
p-value[b]	0.0001	
CR n (%)	9 (12)	15 (10)
PR n (%)	29 (40)	61 (42)
nCR n (%)	7 (10)	14 (10)
Intent to Treat Population[c]	**N=74**	**N=148**
Median Time to Progression, months	9.4	10.4
(95% CI)	(7.6, 10.6)	(8.5, 11.7)
Hazard ratio (95% CI)[d]	0.839 (0.564, 1.249)	
p-value (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)[d]	0.824 (0.574, 1.183)	
p-value[e]	0.295	
1-year Overall Survival (%)[f]	76.7	72.6
(95% CI)	(64.1, 85.4)	(63.1, 80.0)

[a] All randomised subjects who received at least 1 non-zero dose of study medication and had measurable disease at study entry.
[b] P-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in the IV arm.
[c] 222 subjects were enrolled into the study; 221 subjects were treated with Bortezomib.
[d] Hazards ratio estimate is based on a Cox model adjusted for stratification factors: ISS staging and number of prior lines.
[e] Log-rank test adjusted for stratification factors: ISS staging and number of prior lines.
[f] Median duration of follow up is 11.8 months.

Table 19 presents a cross-tabulation summary of best response by algorithm after 4 cycles versus after 8 cycles for patients who received dexamethasone. Eighty-two subjects in the SC treatment group and 39 subjects in the IV treatment group received dexamethasone after Cycle 4.

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

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

Table 19: Cross-tabulation of Summary of Best Response After 4 Cycles vs. After 8 Cycles for Patients Who Received Dexamethasone

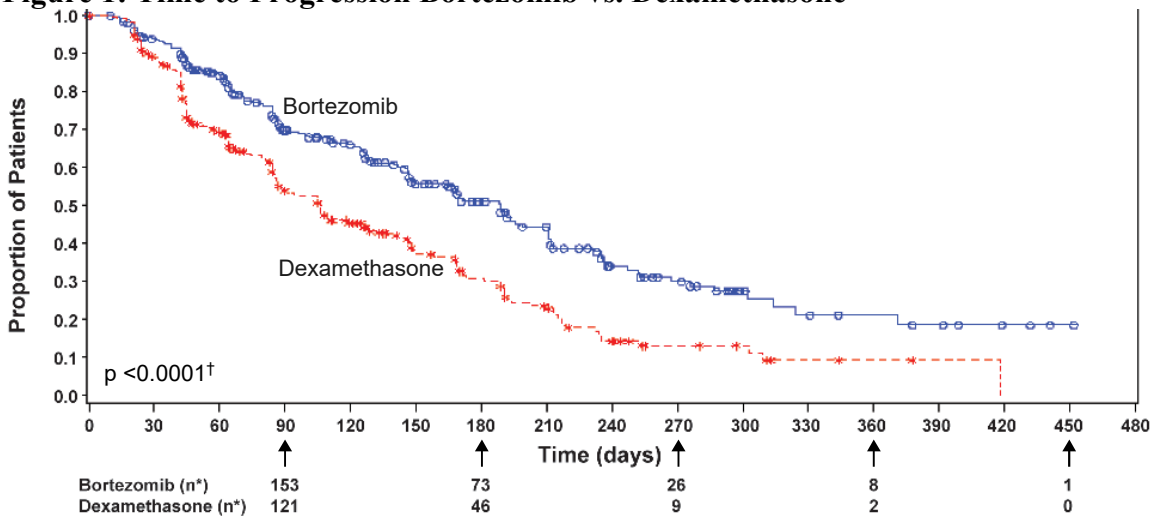
		Best Response After 8 Cycles (N=121)		
Treatment Group	Total	Category, n (%)		
Cycle 4 Best Response[a]	n (%)	CR	PR	Non-responder
IV	39 (32)	3 (8)	20 (51)	16 (41)
CR	1 (1)	1 (100)	0	0
PR	15 (12)	2 (13)	13 (87)	0
Non-responder	23 (19)	0	7 (30)	16 (70)
SC	82 (68)	8 (10)	41 (50)	33 (40)
CR	4 (3)	4 (100)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

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

Relative to previously reported outcomes, the ORR after 8 cycles of treatment (52% in both treatment groups) and time to progression (median 10.4 months and 9.4 months in SC and IV treatment groups, respectively), including the effect of the addition of dexamethasone from Cycle 5 onwards, were higher than observed in prior registration study with single agent IV Bortezomib (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 that received only 1 prior line of therapy (43% ORR and median TTP of 7.0 months) (Table 16).

TTP was statistically significantly longer on the Bortezomib arm (see Figure 1).

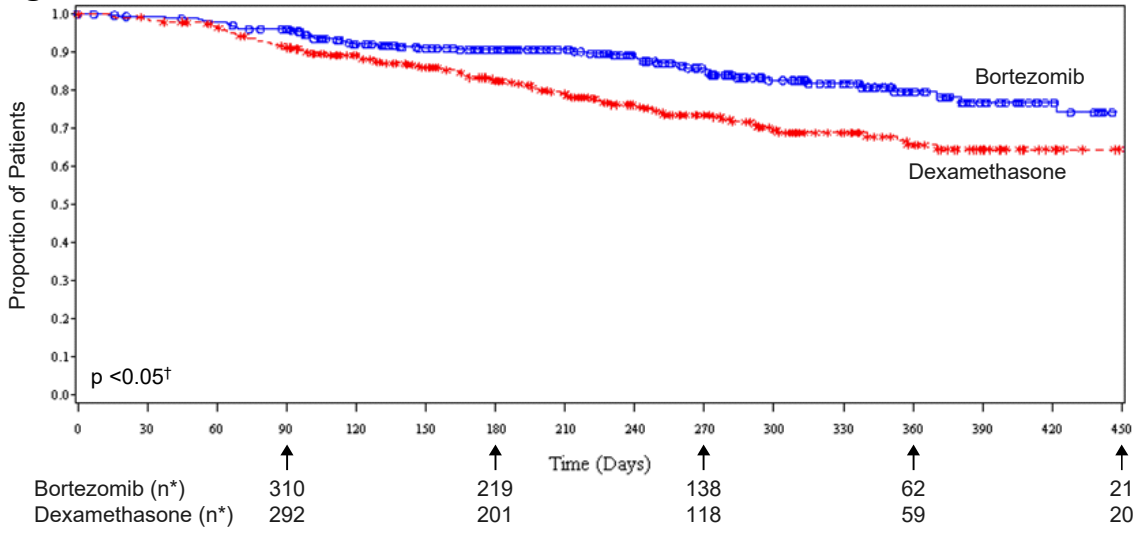
Figure 1: Time to Progression Bortezomib vs. Dexamethasone



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

As shown in Figure 2, Bortezomib had a significant survival advantage relative to dexamethasone ($p<0.05$). The median follow-up was 8.3 months.

Figure 2: Overall Survival Bortezomib vs. Dexamethasone



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

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

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

An open-label, multicentre study randomised 54 patients with multiple myeloma who had progressed or relapsed on or after front-line therapy to receive Bortezomib 1.0 mg/m^2 or 1.3 mg/m^2 IV bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). The median duration of time between diagnosis of multiple myeloma and first dose of Bortezomib on this trial was 2.0 years, and patients had received a median of 1 prior line of treatment (median of 3 prior therapies). A single complete response was seen at each dose. The overall response rates (CR + PR) were 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

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

Patients from the two Phase 2 studies who in the investigators' opinion would experience additional clinical benefit continued to receive Bortezomib beyond 8 cycles on an extension study. Sixty-three (63) patients from the Phase 2 multiple myeloma studies were enrolled and received a median of 7 additional cycles of Bortezomib therapy for a total median of 14 cycles (range 7 to 32). The overall median dosing intensity was the same in both the parent protocol and extension study. Sixty-seven percent (67%) of patients initiated the extension study at the same or higher dose intensity at which they completed the parent protocol, and 89% of patients maintained the standard 3-week-dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed with prolonged Bortezomib treatment (see section 4.8).

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

A prospective Phase 3, international, randomised (1:1), open-label clinical study of 682 patients was conducted to determine whether Bortezomib (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) (B+M+P) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. This study included patients who were not candidates for stem cell transplant. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarised in Table 20.

Table 20: Summary of Baseline Patient and Disease Characteristics in the VISTA Study

Patient Characteristics	**B+M+P N=344**	**M+P 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%
Haemoglobin <100 g/L	37%	36%
Platelet count <75 x 10^9/L	<1%	1%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	64% / 24% / 8%	62% / 26% / 8%
Median β_2-microglobulin (mg/L)	4.2	4.3
Median albumin (g/L)	33.0	33.0
Creatinine clearance ≤30 mL/min [n (%)]	20 (6%)	16 (5%)

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the M+P arm were offered B+M+P treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up at 60.1 months. A statistically significant survival benefit in favour of the B+M+P treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies that included Bortezomib-based regimens. The median survival in M+P treatment group has been estimated at 43.1 months, and the median survival on the B+M+P treatment group has been estimated at 56.4 months. Efficacy results are presented in Table 21.

Table 21: Summary of Efficacy Analyses in the VISTA study

Efficacy Endpoint	**B+M+P n=344**	**M+P n=338**
Time to Progression		
Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24.7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value[c]	0.000002	
Progression-free Survival		
Events n (%)	135 (39)	190 (56)

Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value[c]	0.00001	
Overall Survival[h] Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median[a] (95% CI)	56.4 mo (52.8, 60.9)	43.1 mo (35.3, 48.3)
Hazard ratio[b] (95% CI)	0.695 (0.567, 0.852)	
p-value[c]	0.00043	
Response Rate population[e] n=668	n=337	n=331
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR + PR[f] n (%)	238 (71)	115 (35)
p-value[d]	$<10^{-10}$	
Reduction in Serum M-protein population[g] n=667	n=336	n=331
≥90% n (%)	151 (45)	34 (10)
Time to First Response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] Response Duration		
CR[f]	24.0 mo	12.8 mo
CR + PR[f]	19.9 mo	13.1 mo
Time to Next Therapy Events n (%)	224 (65.1)	260 (76.9)
Median[a] (95% CI)	27.0 mo (24.7, 31.1)	19.2 mo (17.0, 21.0)
Hazard ratio[b] (95% CI)	0.557 (0.462, 0.671)	
p-value[c]	(<0.000001)	

Note: All results are based on the analysis performed at a median follow-up duration of 16.3 months except for the overall survival analysis that was performed at a median follow-up duration of 60.1 months.

[a] Kaplan-Meier estimate.

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

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

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

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

[f] EBMT criteria.

[g] All randomised patients with secretory disease.

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

NE: Not estimable.

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

The safety and efficacy of Bortezomib in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicentre study [M34103-053 (PINNACLE)] of 155 patients with progressive disease who had received at least 1 prior therapy. Bortezomib was administered at the recommended dose of 1.3 mg/m^2. The median number of cycles administered across all patients was 4 (range 1-17); and 8 in responding patients. Response rates to Bortezomib are described in Table 22.

Table 22: Summary of Disease Outcomes in a Phase 2 Mantle Cell Lymphoma Study

[a]**Response Analyses (N=141)**	**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu + PR)	47 (33)	(26, 42)
Complete Response (CR + CRu)	11 (8)	(4, 14)
CR	9 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (26)	(19, 34)
Time to Event Analyses	Median	95% CI
Kaplan-Meier Estimated Duration of Response		
CR + CRu + PR (N=47)	9.2 months	(4.9, 13.5)
CR + CRu (N=11)	13.5 months	(13.5, NE)
Kaplan-Meier Estimated Time to Progression (N=155)	6.2 months	(4.0, 6.9)
**Kaplan-Meier Estimated Treatment Free Interval, CR + CRu (N=11)	13.8 months	(13.4, NE)
Median Time to Next Treatment		
CR + CRu + PR (N=47)	12.7 months	(9.33, NE)
CR + CRu (N=11)	19.4 months	(17.8, NE)

[a] Based on International Response Workshop Criteria (IRWC).
CRu=Complete Response unconfirmed.
NE=Not estimable.
** Additional analyses.

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

Previously Untreated Mantle Cell Lymphoma

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

Patients in the BR-CAP treatment arm received Bortezomib (1.3 mg/m^2) administered intravenously on Days 1, 4, 8, and 11 (rest period Days 12-21); rituximab (375 mg/m^2) on

Day 1; cyclophosphamide (750 mg/m^2) on Day 1; doxorubicin (50 mg/m^2) on Day 1; and prednisone (100 mg/m^2) on Day 1 through Day 5 of the 21-day treatment cycle. For patients with a response first documented at Cycle 6, two additional treatment cycles were given.

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

The primary efficacy endpoint was progression-free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti-lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration. The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC).

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

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

Efficacy results are presented in Table 23.

Table 23: Summary of Efficacy Outcomes in a Phase 3 Mantle Cell Lymphoma Study in Previously Untreated Patients (LYM-3002)

Efficacy endpoint	**BR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7)	165 (67.6)	HR[d] (95% CI)=0.63 (0.50;0.79) p-value[e] <0.001
Median[c] (95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	
Progression free survival (Investigator)[b]			
Events n (%)	128 (52.7)	179 (73.4)	HR[d] (95% CI)=0.51 (0.41; 0.65) p-value[e] <0.001
Median[c] (95% CI) (months)	30.7 (25.1; 37.3)	16.1 (14.0; 18.4)	

Efficacy endpoint	**BR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Time to Progression[a]			
Events n (%)	114 (46.9)	148 (60.7)	HR[d] (95% CI)=0.58 (0.45;0.74) p-value[e] <0.001
Median[c] (95% CI) (months)	30.5 (22.9; 40.9)	16.1(13.7;18.1)	
Time to Next Anti-lymphoma Therapy			
Events n (%)	94 (38.7)	145 (59.4)	HR[d] (95% CI)=0.50 (0.38;0.65) p-value[e] <0.001
Median[c] (95% CI) (months)	44.5 (38.8; NE)	24.8 (22.1; 27.5)	
Treatment Free Interval			
n: All Treated Patients	240	242	
Events n (%)	93 (38.8)	145 (59.9)	HR[d] (95% CI)=0.50 (0.38; 0.65) p-value[e] <0.001
Median[c] (95% CI) (months)	40.6 (33.6; NE)	20.5 (17.8; 22.8)	
Overall survival at a median follow-up of 82 months			
n: ITT patients	243	244	
Events n (%)	103 (42.4)	138 (56.6)	HR[d] (95% CI)=0.66 (0.51; 0.85) p-value[e] =0.001
Median[c] (95% CI) (months)	90.7 (71.4; NE)	55.7 (47.2; 68.9)	
Response Rate			
n: response-evaluable patients	229	228	
Overall complete response (CR+CRu)[h] n(%)	122 (53.3)	95 (41.7)	OR[f] (95% CI)=1.688 (1.148; 2.481) p-value[g] =0.007
Overall radiological response (CR+CRu+PR)[i] n(%)	211 (92.1)	204 (89.5)	OR[f] (95% CI)=1.428 (0.749; 2.722) p-value[g] =0.275
Response Duration			
Duration of complete response (CR+CRu)[j]			
n=response-evaluable patients	122	95	
Median[c] (95% CI) (months)	42.1 (30.7; 49.1)	18.0 (14.0; 23.4)	
Duration of Response (CR+CRu+PR)[k]			
n: response-evaluable subjects	211	204	
Median[c] (95% CI) (months)	36.5 (26.7; 46.7)	15.1 (12.5; 17.0)	

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

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

[b] Based on Investigator assessment.

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

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

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

[f] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and Stage of Disease as stratification factors. An odds ratio (OR) >1 indicates an advantage for BR-CAP.

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

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

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

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

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

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

Patients with Previously Treated Light-Chain (AL) Amyloidosis

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

5.2 Pharmacokinetic properties

Absorption

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 3 trial, following an IV bolus or subcutaneous (SC) injection of a 1.3 mg/m^2 dose to multiple myeloma patients (n=14 for IV, n=17 for SC), the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent (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 1884 L/m^2) following single- or repeat-dose IV 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.

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 and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. 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 IV 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*.

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. Clearance of bortezomib was comparable among all the groups. However, the number of patients with severe renal impairment was insufficient to allow reliable conclusions regarding this group (see section 4.4).

Hepatic Impairment

Formal studies in patients with severely impaired hepatic function have not been conducted to date; consequently caution is recommended when administering bortezomib to these classes of patients (see section 4.4).

5.3 Preclinical safety data

Genotoxicity

Bortezomib showed genotoxic potential. Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) 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 positive when tested in the *in vitro* tests for bacterial gene mutation.

Carcinogenicity

Carcinogenicity studies have not been conducted with bortezomib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

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

Reconstituted solution: Pfizer Bortezomib Powder for Injection 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 under normal lighting conditions 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.

6.4 Special precautions for storage

Unopened vials: Store below 30°C. Keep the container in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pfizer Bortezomib Powder for Injection 3.5 mg is supplied as white, to off white lyophilised powder in a 10 mL, type I, clear glass vial with grey butyl stopper and aluminium seal. Each vial contains 38.5 mg powder (3.5 mg bortezomib) for solution for IV or SC injection.

Pfizer Bortezomib Powder for Injection is available in cartons containing 1 vial. Product is for single use in one patient only.

6.6 Special precautions for disposal and other handling

Instructions for Use and Handling and Disposal

Administration Precautions*:* Bortezomib 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 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. Bortezomib is for IV and subcutaneous use only. **DO NOT ADMINISTER BORTEZOMIB INTRATHECALLY**.

Reconstitution/Preparation for 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
	3.5 mg bortezomib	3.5 mg bortezomib
Volume of diluent (0.9% Sodium Chloride) added to reconstitute one vial	3.5 mL	1.4 mL
Final concentration after reconstitution (mg/mL)	1.0 mg/mL	2.5 mg/mL

The reconstituted product should be a clear and colourless solution.

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.

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