PACKAGE INSERT –
BORTEZOMIB-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL
(Bortezomib)

1. NAME OF THE MEDICINE

BORTEZOMIB-AFT POWDER FOR SOLUTION FOR INJECTION 3.5 MG/VIAL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BORTEZOMIB-AFT (bortezomib) 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. It also contains 35 mg mannitol.

For a full list of excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Powder for injection. White to off-white cake or 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 drug substance exists in its cyclic anhydride form as a trimeric boroxine.

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

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.

Once reconstituted with sodium chloride 9 mg/mL, BORTEZOMIB-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL is practically free from visible particulates.

BORTEZOMIB-AFT contains no antimicrobial agents.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

BORTEZOMIB-AFT is indicated as part of combination therapy for the treatment of patients with previously untreated multiple myeloma.

BORTEZOMIB-AFT is indicated as monotherapy for the treatment of patients with multiple myeloma who have received at least 1 prior therapy.

BORTEZOMIB-AFT is indicated as monotherapy for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

BORTEZOMIB-AFT 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. DOSE AND METHOD OF ADMINISTRATION

BORTEZOMIB-AFT 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 BORTEZOMIB-AFT .

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

Monotherapy

Relapsed/refractory multiple myeloma and relapsed/refractory mantle cell lymphoma (MCL)

Recommended dose

The recommended dose of BORTEZOMIB-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL 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-AFT .

For extended therapy of more than 8 cycles, BORTEZOMIB-AFT may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (days 1, 8, 15, and 22) followed by a 13-day rest period (days 23 – 35) (see **Section 5.1 Pharmacodynamic properties, Clinical trials** for a summary of dose administration during clinical trials).

Dose modification and re-initiation of therapy

BORTEZOMIB-AFT therapy should be withheld at the onset of any Grade 3 non-haematological or Grade 4 haematological toxicities excluding neuropathy (see **Section 4.4 Special warnings and precautions for use**). Once the symptoms of the toxicity have resolved, BORTEZOMIB-AFT therapy may be re-initiated 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 1 contains the recommended dose modification for the management of patients who experience BORTEZOMIB-AFT -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-AFT only after careful risk/benefit assessment.

Table 1: Recommended dose modification for BORTEZOMIB-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL - 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-AFT to 1.0 mg/m^2 OR change BORTEZOMIB-AFT 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-AFT therapy until toxicity resolves. When toxicity resolves re-initiate with a reduced dose of BORTEZOMIB-AFT at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue BORTEZOMIB-AFT

* *Grading based on NCl 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.*

Combination therapy

Previously untreated multiple myeloma – Non-transplant eligible

Recommended dosage in combination with melphalan and prednisone

BORTEZOMIB-AFT (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in **Table 2**. In cycles 1 – 4, BORTEZOMIB-AFT is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In cycles 5 – 9, BORTEZOMIB-AFT is administered once weekly (days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of BORTEZOMIB-AFT .

Table 2: Recommended dosage regimen for BORTEZOMIB-AFT when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma

Twice weekly BORTEZOMIB-AFT (Cycles 1 – 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
BA (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-AFT (Cycles 5 – 9)									
Week	**1**				**2**	**3**	**4**	**5**	**6**
BA (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

BA = BORTEZOMIB-AFT ; m = melphalan; p = prednisone

Dose management guidelines

Dose modification and re-initiation of therapy when BORTEZOMIB-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL is administered in combination with melphalan and prednisone.

Prior to initiating a new cycle of therapy:

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

Table 3: 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-AFT dosing day (other than day 1)	BORTEZOMIB-AFT dose should be withheld
• If several BORTEZOMIB-AFT doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	BORTEZOMIB-AFT dose should be reduced by 1 dose level (from 1.3 – 1 mg/m^2, or from 1 – 0.7 mg/m^2)
Grade ≥ 3 non-haematological toxicities	BORTEZOMIB-AFT therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, BORTEZOMIB-AFT may be re-initiated 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-AFT -related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTEZOMIB-AFT as outlined in **Table 1**.

For additional information concerning melphalan and prednisone, see manufacturer's Product Information documents.

Previously untreated mantle cell lymphoma – Non-transplant eligible

Recommended dosage in combination with rituximab, cyclophosphamide, doxorubicin and prednisone

BORTEZOMIB-AFT (bortezomib) 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-AFT cycles are recommended, although for patients with a response first documented at cycle 6, two additional BORTEZOMIB-AFT cycles may be given. At least 72 hours should elapse between consecutive doses of BORTEZOMIB-AFT .

The following medicinal products are administered on Day 1 of each BORTEZOMIB-AFT 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 (other than cycle 1):

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

BORTEZOMIB-AFT treatment must be withheld at the onset of any ≥ Grade 3 BORTEZOMIB-AFT - related non haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities (see also **Section 4.4 Special warnings and precautions for use**). 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-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL 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-AFT has been held, the toxicity does not resolve, as defined above, then BORTEZOMIB-AFT 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-AFT dose should be 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-AFT dosing day (other than Day 1 of each cycle)	BORTEZOMIB-AFT dose should be withheld

Toxicity	**Posology modification or delay**
Grade ≥ 3 non-hematological toxicities	BORTEZOMIB-AFT therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then BORTEZOMIB-AFT may be re-initiated 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-AFT -related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTEZOMIB-AFT as outlined in **Table 1**.

In addition, when BORTEZOMIB-AFT 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.

Method of administration

Intravenous injection (IV)

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

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

Instructions for use and handling and disposal

Administration precautions:

BORTEZOMIB-AFT is an antineoplastic. Caution should be used during handling and preparation, including careful dose calculation to prevent overdose. The drug quantity in one vial (3.5 mg) may exceed the usual single dose required. 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-AFT is for IV and subcutaneous use only. **DO NOT ADMINISTER BORTEZOMIB-AFT INTRATHECALLY.**

Reconstitution/Preparation for administration for intravenous and subcutaneous 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:

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

Dosage adjustment in:

Patients with Renal Impairment

The pharmacokinetics of bortezomib are not influenced by the degree of renal impairment. Therefore,

dosing adjustments of bortezomib are not necessary for patients with renal insufficiency. Since dialysis may reduce bortezomib concentrations, the drug should be administered after the dialysis procedure (see section 5.2 Pharmacokinetic Properties).

Hepatic insufficiency

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended BORTEZOMIB-AFT dose. Patients with moderate or severe hepatic impairment should be started on BORTEZOMIB-AFT 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-AFT in patients with hepatic impairment

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

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

4.3. CONTRAINDICATIONS

BORTEZOMIB-AFT is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol. BORTEZOMIB-AFT is also contraindicated in patients with acute diffuse infiltrative pulmonary and pericardial disease.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

There have been fatal cases of inadvertent intrathecal administration of bortezomib. BORTEZOMIB-AFT is for intravenous or subcutaneous use only. **DO NOT ADMINISTER BORTEZOMIB-AFT 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.

<u>Peripheral neuropathy</u>

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 were 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-AFT 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 Dose and method of administration**).

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 Adverse effects (undesirable effects)**).

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.

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, patients 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 Adverse effects (undesirable effects)**).

Cardiac disorders

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported, including reports in patients with few or no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or an existing heart disease should be closely monitored. In the Phase 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.

Thrombotic microangiopathy

There have been cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) reported in patients who received proteasome inhibitors. Some of these events have been fatal. Patients receiving BORTEZOMIB-AFT should be monitored for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop BORTEZOMIB-AFT and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, BORTEZOMIB-AFT can be re-initiated. The safety of re-initiating BORTEZOMIB-AFT therapy in patients previously experiencing TTP/HUS is not known.

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-AFT . The safety of re-initiating BORTEZOMIB-AFT
therapy in patients previously experiencing PRES is not known.

Seizures

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

Patients with previously treated light-chain (AL) 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, and in particular bortezomib did not exacerbate target organ damage (heart, kidney and liver). In 49 evaluable patients treated at 1.6 mg/m2 weekly or 1.3 mg/m2 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%.

Laboratory tests

Complete blood counts (CBC) should be frequently monitored throughout treatment with BORTEZOMIB-AFT .

Thrombocytopenia/neutropenia

BORTEZOMIB-AFT treatment is associated with thrombocytopenia and neutropenia (see **Section 4.8 Adverse effects (undesirable effects)**). 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-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL. BORTEZOMIB-AFT therapy should be held when the platelet count is < 25,000/µL (see **Sections 4.2 Dose and method of administration** and **Section 4.8 Adverse effects (undesirable effects)**). There have been reports of gastrointestinal and intracerebral hemorrhage 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 single agent APEX (Phase 3) multiple myeloma 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.*
*** Date 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 (VcR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia adverse events (≥ Grade 4) was 32% versus 2% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm. The incidence of bleeding adverse events (≥ Grade 3) was 1.7% (4 patients) in the VcR-CAP arm and was 1.2% (3 patients) in the R-CHOP arm.

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

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

Gastrointestinal adverse events

BORTEZOMIB-AFT treatment can cause nausea, diarrhoea, constipation and vomiting (see **Section 4.8 Adverse effects (undesirable effects)**) sometimes requiring use of antiemetics and antidiarrhoeals. Fluid and electrolyte replacement should be administered to prevent dehydration. Since patients receiving BORTEZOMIB-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL therapy may experience vomiting and/or diarrhoea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

Tumour Lysis syndrome

Because BORTEZOMIB-AFT 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.

Herpes Zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with BORTEZOMIB-AFT (see **Section 4.8 Adverse effects (undesirable effects)**).

Multiple myeloma

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

Mantle cell lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the VcR-CAP arm. The incidence of herpes zoster among patients in the VcR-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-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL, 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-AFT . Antiviral prophylaxis should be considered. Refer to the local Product Information of rituximab for more information.

Hepatic events

Rare cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic events include increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of BORTEZOMIB-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL. There is limited re-challenge information in these patients.

Use in hepatic impairment

Patients with moderate and severe hepatic impairment should be treated with caution at reduced starting doses of BORTEZOMIB-AFT and closely monitored for toxicities (see **Section 4.2 Dose and method of administration, Dosage adjustment in: Hepatic insufficiency** and **Section 5.2**

Pharmacokinetic properties, Special populations, Hepatic impairment). The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in 51 cancer patients with varying degrees of hepatic impairment treated bortezomib doses ranging from 0.5 – 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.

Use in 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 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.

Use in 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 VcR-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.

Use in the elderly

See Section 5.1 Pharmacodynamic properties, Geriatric use.

Paediatric use

The safety and effectiveness of BORTEZOMIB-AFT in children has not been established.

Effects on laboratory tests

None known.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro and animal *ex vivo* studies indicate that bortezomib is a weak inhibitor of cytochrome P450 (CYP) 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-AFT 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.

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

Patients who are concomitantly receiving BORTEZOMIB-AFT and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy. Caution should be exercised when bortezomib is combined with CYP3A4 or CYP2C19 substrates. Normal liver functions should be confirmed and caution should be exercised in patients receiving oral hypoglycemic.

During clinical trials, hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic agents receiving BORTEZOMIB-AFT treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies with bortezomib were not performed but degenerative changes seen in the testes and

ovary in a rat general toxicity study suggest that BORTEZOMIB-AFT SOLUTION FOR INJECTION 3.5 MG/VIAL may affect male and female fertility.

Use in pregnancy – Category C

Women of child bearing potential should avoid becoming pregnant while being treated with BORTEZOMIB-AFT . 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-AFT is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the foetus.

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

Use in lactation

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

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

BORTEZOMIB-AFT may cause tiredness, dizziness, fainting, orthostatic/postural hypotension or blurred vision. Patients should be advised not to drive or operate machinery if they experience these symptoms.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events

Summary of clinical trials of bortezomib IV in patients with previously untreated multiple myeloma:

Results from the VISTA study

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

Table 7 : Treatment emergent drug-related adverse events reported in ≥ 10% of patients treated with bortezomib IV in combination with melphalan and prednisone

	VcMP (n = 340)			**MP (n = 337)**		
MedDRA System Organ Class Preferred term	Total n (%)	Toxicity grade, n (%) 3	≥ 4	Total n (%)	Toxicity grade, 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)	7 (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

Antiviral prophylaxis is recommended in patients being treated with BORTEZOMIB-AFT . In the VISTA study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with VcMP compared with MP (14% vs 4% respectively). Antiviral prophylaxis was administrated to 26% of the patients in the VcMP arm. The incidence of herpes zoster among patients in the VcMP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Summary of clinical trials of bortezomib IV in patients with relapsed/refractory multiple myeloma:

The safety and efficacy of bortezomib IV 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, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy (M34100-025); and a Phase 2 dose-response clinical study in relapsed multiple myeloma for patients who had progressed or relapsed on or after first line therapy with bortezomib IV 1.0 mg/m^2 or 1.3 mg/m^2 (M34100-024).

Table 8: Bortezomib IV 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 & 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%)

	Study No.	
MedDRA System Organ Class Preferred term	039 (n = 331)	024/025 (n = 228[a])
Dyspepsia	32 (10%)	30 (13%)
Pharyngolaryngeal pain	25 (8%)	19 (8%)
Gastroesophageal reflux	10 (3%)	1 (< 1%)
Eructation	2 (< 1%)	4 (2%)
Abdominal distension	14 (4%)	13 (6%)
Stomatitis and mouth ulceration	24 (7%)	10 (4%)
Dysphagia	4 (1%)	5 (2%)
GI hemorrhage (upper and lower GI tract)[b]	7 (2%)	3 (1%)
Rectal hemorrhage (includes hemorrhagic diarrhoea)	7 (2%)	3 (1%)
Tongue ulceration	2 (< 1%)	1 (< 1%)
Retching	3 (< 1%)	2 (< 1%)
Upper GI hemorrhage	1 (< 1%)	---
Hematemesis	1 (< 1%)	---
Oral mucosal petechiae	3 (< 1%)	---
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		
Hyperbilirubinemia	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%)

	Study No.	
MedDRA System Organ Class Preferred term	039 (n = 331)	024/025 (n = 228[a])
Bronchitis	26 (8%)	6 (3%)
Postherpetic neuralgia	4 (1%)	1 (< 1%)
Sinusitis	14 (4%)	15 (7%)
Pharyngitis	6 (2%)	2 (< 1%)
Oral candidiasis	6 (2%)	3 (1%)
Urinary tract infection	13 (4%)	14 (6%)
Catheter related infection	10 (3%)	6 (3%)
Sepsis and bacteremia[b]	9 (3%)	9 (4%)
Gastroenteritis	7 (2%)	---
Injury, poisoning, and procedural complications		
Catheter related complication	7 (2%)	8 (4%)
Investigations		
Increased ALT	3 (< 1%)	10 (4%)
Increased AST	5 (2%)	12 (5%)
Increased alkaline phosphatase	6 (2%)	8 (4%)
Increased GGT	1 (< 1%)	4 (2%)
Metabolism and nutritional disorders		
Decreased appetite and anorexia	112 (34%)	99 (43%)
Dehydration	24 (7%)	42 (18%)
Hyperglycemia	5 (2%)	16 (7%)
Hypoglycemia	7 (2%)	4 (2%)
Hyponatremia	8 (2%)	18 (8%)
Tumor Lysis Syndrome	2 (< 1%) in study M34101-040[c]	---
Musculoskeletal and connective tissue disorders		
Pain in limb	50 (15%)	59 (26%)
Myalgia	39 (12%)	32 (14%)
Arthralgia	45 (14%)	60 (26%)
Nervous system disorders		
Peripheral neuropathy[d]	120 (36%)	84 (37%)
Paresthesia and dysesthesia	91 (27%)	53 (23%)
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		

	Study No.	
MedDRA System Organ Class Preferred term	039 (n = 331)	024/025 (n = 228[a])
Renal impairment and failure	21 (6%)	21 (9%)
Difficulty in micturition	2 (1%)	3 (1%)
Hematuria	5 (2%)	4 (2%)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	21 (6%)	23 (10%)
Cough	70 (21%)	39 (17%)
Dyspnoea	65 (20%)	50 (22%)
Exertional dyspnoea	21 (6%)	18 (8%)
Pleural effusion	4 (1%)	9 (4%)
Rhinorrhoea	4 (1%)	14 (6%)
Hemoptysis	3 (< 1%)	2 (< 1%)
Skin and subcutaneous tissue disorders		
Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vasculitis	61 (18%)	47 (21%)
Urticaria	7 (2%)	5 (2%)
Vascular disorders		
Hypotension	20 (6%)	27 (12%)
Orthostatic/postural hypotension	14 (4%)	8 (4%)
Petechiae	6 (2%)	7 (3%)
Cerebral hemorrhage[b]	1 (< 1%)	---

[a] All 228 patients received bortezomib IV at a dose of 1.3 mg/m².

[b] Includes fatal outcome.

[c] A study of bortezomib IV at the recommended dose of 1.3 mg/m² 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".

The adverse events most commonly reported, regardless of causality, in the APEX study in relapsed/refractory multiple myeloma patients (see **Section 5.1 Pharmacodynamic properties, Clinical trials**) are presented in **Table 9**. All adverse events occurring at ≥ 10% are included.

Table 9: Most commonly reported (≥ 10% in bortezomib arm) adverse events in the APEX study using the 1.3 mg/m² dose (n = 663)

	Bortezomib (n = 331)			**Dexamethasone (n = 332)**		
	All Events %	**Grade 3 %**	**Grade 4 %**	**All Events %**	**Grade 3 %**	**Grade 4 %**
Adverse event	**100**	**61**	**14**	**98**	**44**	**16**
Body as a whole – General disorders						
Asthenic conditions (fatigue, malaise, weakness)	61	12	< 1	45	6	0
Pyrexia	35	2	0	16	1	< 1
Rigors	11	0	0	2	0	0
Oedema lower limb	11	0	0	13	< 1	0
Gastrointestinal system disorders						

	Bortezomib (n = 331)			Dexamethasone (n = 332)		
	All Events %	Grade 3 %	Grade 4 %	All Events %	Grade 3 %	Grade 4 %
Diarrhoea	57	7	0	21	2	0
Nausea	57	2	0	14	0	0
Constipation	42	2	0	15	1	0
Vomiting	35	3	0	6	1	0
Abdominal pain	16	2	0	4	< 1	0
Central & peripheral nervous system disorders						
Peripheral neuropathy*	36	7	< 1	9	< 1	< 1
Paraesthesia and dysaesthesia	27	2	0	11	< 1	0
Headache	26	< 1	0	13	< 1	0
Dizziness (excluding vertigo)	14	< 1	0	10	0	0
Blood & lymphatic system disorders						
Thrombocytopenia	35	26	4	11	5	1
Anaemia	26	9	< 1	22	10	< 1
Neutropenia	19	12	2	2	1	0
Psychiatric disorders						
General	35	3	< 1	49	5	1
Insomnia	18	< 1	0	27	2	0
Metabolism and nutritional disorders						
Appetite decreased and anorexia	34	3	0	9	< 1	0
Respiratory system disorders						
Cough	21	< 1	0	11	< 1	0
Dyspnoea	20	5	< 1	17	3	< 1
Skin and subcutaneous tissue disorders						
Rash	18	1	0	6	0	0
Infections and infestations						
Lower respiratory/lung infections	15	4	< 1	21	5	< 1
Nasopharyngitis	14	< 1	0	7	0	0
Herpes zoster	13	2	0	5	1	< 1
Musculoskeletal and connective tissue disorders						
Bone pain	16	4	0	15	3	0
Pain in limb	15	2	0	7	< 1	0
Back pain	14	3	0	10	1	0
Arthralgia	14	< 1	0	11	2	0
Muscle cramps	12	0	0	15	< 1	0
Myalgia	12	< 1	0	5	< 1	0

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

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.

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 10: 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						

	IV (n = 74)			SC (n = 147)		
MedDRA System Organ Class Preferred term	Total n (%)	Toxicity grade, n (%) 3	≥ 4	Total n (%)	Toxicity grade, n (%) 3	≥ 4
Decreased appetite	7 (9)	0	0	14 (10)	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	8 (11)	2 (3)	0	8 (5)	1 (1)	0
Nervous system disorders						
Headache	8 (11)	0	0	5 (3)	0	0
Neuralgia	17 (23)	7 (9)	0	35 (24)	5 (3)	0
Peripheral sensory neuropathy	36 (49)	10 (14)	1 (1)	51 (35)	5 (3)	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 11: 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 MedDRA high level term	TEAE	Toxicity grade, n (%) G ≥ 3	Disc	TEAE	Toxicity grade, n (%) G ≥ 3	Disc
All subjects with TEAE	73 (99)	52 (70)	20 (27)	140 (95)	84 (57)	33 (22)
Gastrointestinal disorders						
Diarrhoea (excl infective)	27 (36)	4 (5)	1 (1)	35 (24)	3 (2)	1 (1)
Gastrointestinal and abdominal pains (excl. oral and throat)	14 (19)	0	0	9 (6)	1 (1)	0
General disorders and administration site conditions						
Asthenic conditions	29 (39)	7 (9)	1 (1)	40 (27)	6 (4)	2 (1)
Infections and infestations						
Upper respiratory tract infections	19 (26)	2 (3)	0	20 (14)	0	0
Nervous system disorders						
Peripheral neuropathies NEC[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 equal to 3; Disc = Discontinuation of any study drug.

Patients who received bortezomib subcutaneously compared to intravenous administration had 13% lower overall incidence of treatment emergent adverse drug reactions that were grade 3 or higher in toxicity (57% vs 70% respectively; *p*-value is 0.0784), and a 5% lower incidence of discontinuation of bortezomib (22% vs 27%; *p*-value is 0.5052). The overall incidence of diarrhoea (24% for the SC

arm vs 36% for the IV arm; *p*-value is 0.0572), gastrointestinal and abdominal pain (6% for the SC arm vs 19% for the IV arm; *p*-value is 0.0049), asthenic conditions (27% for SC arm vs 39% for IV arm), upper respiratory tract infections (14% SC arm vs 26% IV arm; *p*-value is 0.0903) and peripheral neuropathy NEC (38% SC arm vs 53% IV arm; *p*-value is 0.0444) were 12% - 15% lower in the subcutaneous group than the intravenous group. In addition, the incidence of peripheral neuropathies that were grade 3 or higher in toxicity was 10 % lower (6% for SC vs 16% for IV; *p*-value is 0.0264), and the discontinuation rate due to peripheral neuropathies was 8% lower for the subcutaneous group (5%) as compared to the intravenous group (14%); *p*-value is 0.0771.

58 percent of patients (85/147) developed a reaction at the site of subcutaneous injection. Only 2 (1.4%) subjects were reported as having severe reactions. These severe local reactions were 1 case of pruritus and 1 case of redness. These reactions seldom led to dose modifications and all resolved in a median of 6 days (bortezomib treatment modification based on local reactions was needed in 2 subjects (1 treatment discontinuation; 1 drug withholding and reduction in study drug concentration from 2.5 – 1 mg/mL)).

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, anemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and 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 12 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) (VcR-CAP) in a prospective randomised study (LYM-3002).

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

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

HBV infection with fatal outcomes occurred in 0.8% (n = 2) of patients in the non-bortezomib treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) and 0.4% (n = 1) of patients receiving bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP). The overall incidence of hepatitis B infections was similar in patients treated with VcR-CAP or with R-CHOP (0.8% vs 1.2% respectively) (see **Section 4.4 Special warnings and precautions for use**).

In general, the safety profile of bortezomib in mantle cell lymphoma was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (VcR-CAP) were hepatitis B infection (< 1%) and myocardial ischaemia (1.3%). The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to bortezomib alone. Notable differences in the mantle cell lymphoma patient population as compared to patients in the multiple myeloma studies were a ≥ 5% higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.

Table 12: Most commonly reported adverse reactions (≥ 5%) with Grades 3 and ≥ 4 intensity in the mantle cell lymphoma study of VcR-CAP versus R-CHOP (n = 482) (Study LYM-3002)

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

	VcR-CAP (n = 240)			R-CHOP (n = 242)		
System Organ Class Preferred term	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥ 4 n (%)	Total n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥ 4 n (%)
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; VcR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Serious adverse events (SAEs)

Serious adverse events are defined as any event, regardless of causality, that results in death, is life-threatening, required hospitalisation or prolongs a current hospitalisation, results in a significant disability, or is deemed to be an important medical event.

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

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

Non-randomised Phase 2 clinical studies:

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.

Adverse reactions

The following adverse reactions were considered to have at least a possible or probable causal relationship to bortezomib by the investigators during 5 non-comparative Phase 2 studies and 1 comparative Phase 2 trial (APEX) in 663 patients with relapsed or refractory multiple myeloma, of whom 331 received bortezomib as single agent. The safety database comprises data from patients with multiple myeloma or B-cell lymphocytic leukaemia. Patients were treated with bortezomib as a single agent, or in combination with dexamethasone.

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

Infections and infestations

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

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

Blood and lymphatic system disorders

Very common: thrombocytopenia (see **Section 4.4 Special warnings and precautions for use**), anaemia, neutropenia.

Common: leukopenia, lymphopenia.

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

Immune system disorders

Uncommon: hypersensitivity, immunocomplex mediated hypersensitivity.

Metabolism and nutritional disorders

Very common: appetite decreased.

Common: dehydration, hyperglycaemia, hypokalaemia.

Uncommon: hypercalcaemia, hyperkalaemia, hyperuricaemia, hyponatraemia, hypernatraemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia, hypoglycaemia, appetite increased, cachexia, vitamin B12 deficiency, tumour lysis syndrome (see **Section 4.4 Special warnings and precautions for use**).

Endocrine disorders

Uncommon: Inappropriate antidiuretic hormone (ADH) secretion.

Psychiatric disorders

Common: insomnia, anxiety, confusion, depression.

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

Nervous system disorders

Very common: peripheral neuropathy, peripheral sensory neuropathy (see **Section 4.4 Special warnings and precautions for use**), headache, paraesthesia.

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

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

Eye disorders

Common: vision blurred (see **Section 4.4 Special warnings and precautions for use**), eye pain.

Uncommon: dry eye, conjunctivitis, eye discharge, vision abnormal, eye haemorrhage, photophobia, eye irritation, lacrimation increased, conjunctival hyperaemia, eye swelling.

Ear and labyrinth disorders

Common: vertigo.

Uncommon: tinnitus, deafness, hypoacusis, hearing impaired.

Cardiac disorders

Uncommon: development or exacerbation of congestive heart failure (see **Section 4.4 Special warnings and precautions for use**), cardiac failure, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, cardiac arrest, cardiogenic shock, tachycardia, sinus tachycardia, supraventricular tachycardia, arrhythmia, atrial fibrillation, palpitations, sinus arrest, atrioventricular block complete, angina pectoris, angina unstable, myocardial infarction.

Rare: new onset of decreased left ventricular ejection fraction.

Vascular disorders

Common: hypotension, orthostatic and postural hypotension (see **Section 4.4 Special warnings and precautions for use**), phlebitis, haematoma, hypertension.

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

Respiratory, thoracic and mediastinal disorders

Very common: dyspnoea.

Common: epistaxis, dyspnoea exertional, cough, rhinorrhoea.

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

Gastrointestinal disorders *(see* ***Section 4.4 Special warnings and precautions for use****)*

Very common: nausea, diarrhoea, vomiting, constipation.

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

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

Hepatobiliary disorders *(see* ***Section 4.4 Special warnings and precautions for use****)*

Uncommon: hyperbilirubinaemia, hepatitis, hepatic haemorrhage, hypoproteinaemia.

Skin and subcutaneous tissue disorders

Very common: rash.

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

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

Musculoskeletal and connective tissue disorders

Very common: myalgia.

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

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

Renal and urinary disorders

Common: renal impairment, dysuria.

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

General disorders and administration site conditions

Very common: fatigue (see **Section 4.4 Special warnings and precautions for use**), pyrexia.

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

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

Investigations

Common: weight decrease, blood lactate dehydrogenase increased.

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

Injury, poisoning and procedural complications

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

Reproductive system and breast disorders

Uncommon: testicular pain, erectile dysfunction.

Potentially immunocomplex-mediated reactions (see Section 4.4 Special warnings and precautions for use)

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

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with BORTEZOMIB-AFT .

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

Antiviral prophylaxis was administered to 102 of 242 patients (42%) in the R-CHOP arm. The incidence of herpes zoster among patients in the R-CHOP arm was 2.1% for patients not administered antiviral prophylaxis compared to 0% for patients administered antiviral prophylaxis.

Post marketing experience

Clinically significant adverse reactions are listed if they have been reported during post approval use of bortezomib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Blood and lymphatic system disorders	
Rare:	disseminated intravascular coagulation
Very rare:	thrombotic microangiopathy
Cardiac disorders	
Rare:	atrioventricular block complete, cardiac tamponade, pericarditis, ventricular arrhythmias, sinus and ventricular tachycardia
Ear and labyrinth disorders	
Rare:	deafness bilateral
Eye disorders	
Rare:	ophthalmic herpes, optic neuropathy, blindness, chalazion/blepharitis
Gastrointestinal disorders	
Uncommon:	intestinal obstruction
Rare:	ischemic colitis, acute pancreatitis
Hepatobiliary disorders	
Rare:	liver failure
Infections and infestations	
Rare:	herpes meningoencephalitis, septic shock
Very rare:	progressive multifocal leukoencephalopathy[a]
Immune system disorders	
Rare:	angioedema
Very rare:	anaphylactic reaction
Nervous system disorders	
Rare:	encephalopathy, autonomic neuropathy, posterior reversible encephalopathy syndrome
Unknown:	Guillain-Barre Syndrome[b]
Respiratory, thoracic and mediastinal disorders	
Rare:	acute diffuse infiltrative pulmonary disease (see **Section 4.4 Special warnings and precautions for use**), pulmonary hypertension
Skin and subcutaneous tissue disorders	
Rare:	acute febrile neutrophilic dermatosis (Sweet's syndrome)
Very rare:	Stevens-Johnson Syndrome and toxic epidermal necrolysis

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

[b] GBS has been reported in patients treated with bortezomib in the post-market setting with an unknown frequency, causality has not been established.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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 monkeys, doses of 3.0 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at 1 hour post-administration, with progression to death in 12 – 14 hours hollowing drug administration.

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-AFT 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 **Section 4.2 Dose and method of administration** and **Section 4.4 Special warnings and precautions for use**).

For information on the management of overdose, contact the nearest Accident & Emergency department.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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

Previously untreated multiple myeloma

Non-transplant eligible: Randomised, open-label clinical study in patients with previously untreated multiple myeloma

The VISTA study is a prospective Phase 3, international, randomised (1:1), open-label clinical study of 682 patients, conducted to determine whether bortezomib (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma unsuitable for high dose chemotherapy with stem cell transplantation. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Baseline demographics and patient characteristics are summarized in **Table 13**.

Table 13: Summary of baseline patient and disease characteristics in the VISTA study

	VcMP n = 344	**MP n = 338**
Patient characteristics		
Median age in years (range)	71.0 (57, 90)	71.0 (48, 91)
Gender: male/female	51%/49%	49%/51%
Race: Caucasian/Asian/black/other	88%/10%/1%/1%	87%/11%/2%/0%
Karnofsky performance status score ≤ 70	35%	33%
Hemoglobin < 100 g/L	37%	36%
Platelet count < 75 x 10^9/L	< 1%	1%
Disease characteristics		
Type of myeloma (%): IgG/IgA/Light chain	64%/24%/8%	62%/26%/8%
Median β_2-microglobulin (mg/L)	4.2	4.3
Median albumin (g/L)	33.0	33.0
Creatinine clearance ≤ 30 mL/min [n (%)]	20 (6%)	16 (5%)

VcMP = bortezomib + melphalan + prednisone; MP = melphalan + prednisone

At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the MP arm were offered VcMP treatment. Survival continued to be followed after the interim analysis. Median follow-up in the initial analysis (**Table 14**) 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 VcMP treatment group was observed (HR = 0.695; *p* = 0.00043) despite subsequent therapies that included bortezomib-based regimens. Median overall survival in the MP arm was 43.1 months, and the median survival on the VcMP treatment group has been estimated at 56.4 months. Fifty percent of subjects in the MP arm subsequently received bortezomib.

Table 14: Summary of efficacy analyses in the VISTA study

Efficacy endpoint	VcMP n = 344	MP n = 338
Time to progression		
Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24.7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value[c]	0.000002	
Progression-free survival		
Events n (%)	135 (39)	190 (56)
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value[c]	0.00001	
Overall survival		
Events (deaths) n (%)	45 (13)	76 (23)
Hazard ratio[b] (95% CI)	0.61 (0.42, 0.88)	
p-value[c]	0.00782	
Response rate		
Population[e] n = 668	n = 337	n = 331
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR + PR[f] n (%)	238 (71)	115 (35)
p-value[d]	$< 10^{-10}$	
Reduction in serum M-protein		
Population[g] n = 667	n = 336	n = 331
≥ 90% n (%)	151 (45)	34 (10)
Time to first response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] response duration		
CR[f]	24.0 mo	12.8 mo
CR + PR[f]	19.9 mo	13.1 mo
Time to next therapy		
Events n (%)	73 (21)	127 (38)
Median[a] (95% CI)	NE (26.1, NE)	20.8 mo, (18.3, 28.5)
Hazard ratio[b] (95% CI)	0.52 (0.39, 0.70)	
p-value[c]	0.000009	

[a] Kaplan-Meier estimate.

[b] Hazard ratio estimate is based on a Cox proportional-hazart model adjusted for stratification factors: β_2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP.

[c] p-value based on the stratified log-rank test adjusted for stratification factors: β_2-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.

NE: Not estimable

The time to progression (TTP) was significantly longer on the bortezomib arm (see **Figure 1**).

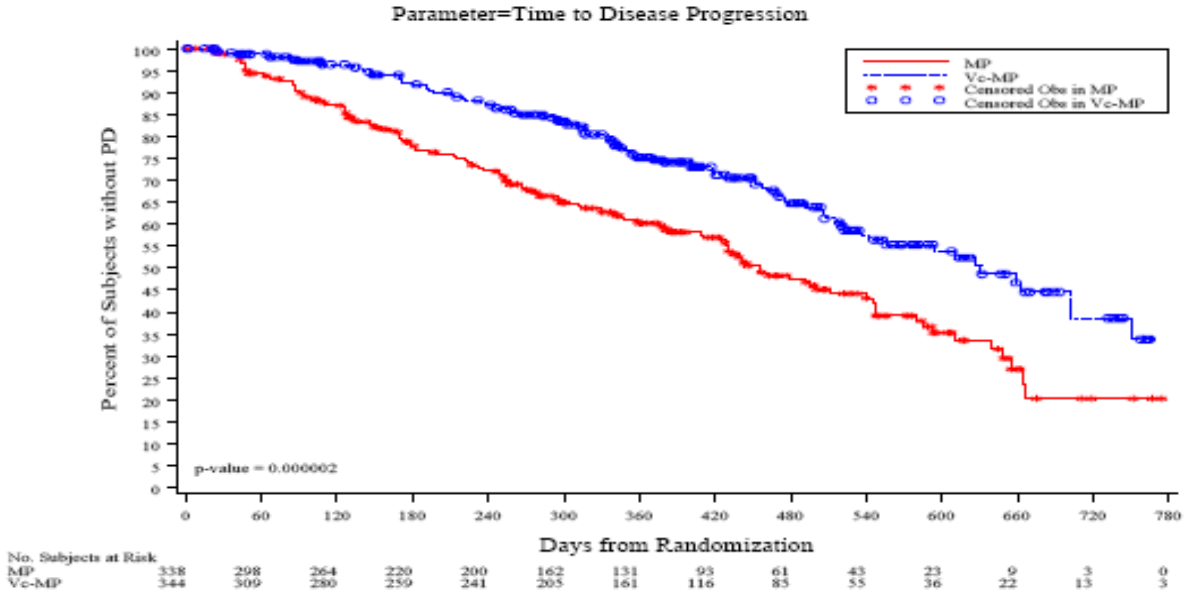


Figure 1: Time to disease progression (Study 26866138-MMY-3002 update: All randomised subjects analysis set)

A significant survival advantage is shown with bortezomib (see **Figure 2**).

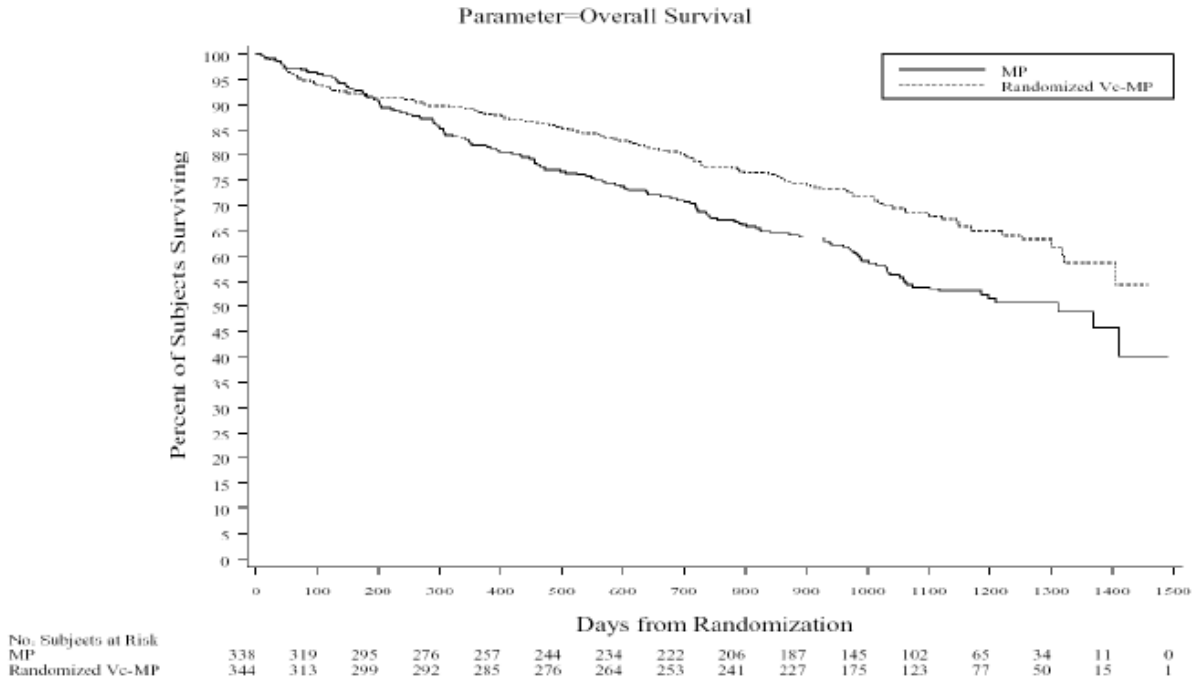


Figure 2: Overall survival (Study 26866138-MMY-3002 update: All randomised subjects analysis set)

Relapsed/Refractory multiple myeloma

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

1 – 3 prior lines of therapy, and a Phase 2 single-arm study of 202 patients with relapsed and refractory multiple myeloma, who had received at least 2 prior lines of treatment and who were progressing on their most recent treatment (see **Table 1 5** and **Table 16**).

Table 15: Dosing regimens in the APEX and Phase 2 studies

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

** a) is the initial treatment, a) and b) represent a full course of treatment*
*** An extension study authorised patients benefiting from treatment to continue receiving bortezomib*
**** If after 2 or 4 cycles of bortezomib, the patients had progressive disease or stable disease, respectively, they could receive dexamethasone*

Table 16: Patient characteristics in the Phase 2* and APEX studies

	Phase 2 study Bortezomib n = 202	**Phase 3 study Bortezomib n = 333**	**Phase 3 study Dex. n = 336**
Patient characteristics			
Median age in years (range)	59 (34 – 84)	62.0 (33 – 84)	61.0 (27 – 86)
Gender: male/female	60%/40%	56%/44%	60%/40%
Race: Caucasian/black/other	81%/10%/8%		
Karnofsky Performance Status score ≤ 70	20%	13%	17%
Haemoglobin < 100 g/L	44%	32%	28%
Platelet count < 75 x 10^9/L	21%	6%	4%
Disease characteristics			
Type of myeloma (%): IgG/IgA/Light chain	60%/24%/14%	60%/23%/12%	59%/24%/13%
Median β_2-microglobulin (mg/L)	3.5	3.7	3.6
Median creatinine clearance (mL/min)	73.9	73.3	75.3
Abnormal cytogenetics	35%		
Chromosome 13 abnormalities	15%	25.7%	25.0%
Median duration of multiple myeloma since diagnosis in years	**4.0**	**3.5**	**3.1**
Previous therapy			
Number of prior therapeutic lines of treatment			
Median (range)**	6 (2 – 15)	2 (1 – 7)	2 (1 – 8)
1 prior line	0	40%	35%
> 1 prior line		60%	65%
All patients			

	Phase 2 study Bortezomib n = 202	Phase 3 study Bortezomib n = 333	Phase 3 study Dex. n = 336
Any prior steroids, e.g. dexamethasone, VAD	99%	98%	99%
Any prior alkylating agents, e.g. MP, VBMCP	92%	91%	92%
Any prior anthracyclines, e.g. VAD, mitoxantrone	81%	77%	76%
Any prior thalidomide therapy	83%	48%	50%
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%	67%	68%
Prior experimental or other types of therapy	44%	3%	2%

** Based on number of patients with baseline data available*

*** Including steroids, alkylating agents, anthracyclines, thalidomide and stem cell transplants*

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 summarized in **Table 17**.

Table 17: Summary of baseline patient and disease characteristics in the Phase 3 trial

	Bortezomib n = 333	Dexamethasone n = 336
Patient characteristics		
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

	Bortezomib n = 333	Dexamethasone n = 336
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤ 30 mL/min [n (%)]	17 (5%)	11 (3%)
Median duration of multiple myeloma since diagnosis in years	**3.5**	**3.1**
Previous therapy		
Number of prior therapeutic lines of treatment		
Median	2	2
1 prior line	40%	35%
> 1 prior line	60%	65%
All patients		
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%
Any 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 Dose and method of administration**).

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 18**. 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 18: 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		< 0.05	
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 in the PR category.*
[g] *In 2 patients, the IF was unknown.*
[h] p-*value for Response rate (CR + PR) from the Cochrane-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 day after bortezomib administration. Patients with baseline grade ≥ 2 peripheral neuropathy or platelet counts < 50,000/µL were excluded. A total of 218 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had received (1 previous line versus more than 1 line of therapy), and international staging system (ISS) stage (incorporating β_2-microglobulin and albumin levels; Stages I, II, or III). The baseline patient and disease characteristics are summarised in **Table 19**.

Table 19: Summary of baseline patient and disease characteristics in the Phase 3 trial of bortezomib IV vs SC

	IV n = 74	**SC n = 148**
Patient characteristics		
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 in years	**2.93**	**2.68**
Previous therapy		
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, with an ORR of 42% in both groups. In addition, all secondary endpoints relating to efficacy showed comparable results between SC and IV administration (**Table 20**).

Table 20: Summary of efficacy analyses for the SC administration of bortezomib compared to IV

	IV bortezomib	SC bortezomib
Response evaluable population	**n = 73**	**n = 145**
Response rate at 4 cycles		
ORR (CR+PR)	31 (42)	61 (42)
p-value[a]	0.00201	
CR n (%)	6 (8)	9 (6)
PR n (%)	25 (34)	52 (36)
nCR n (%)	4 (5)	9 (6)
Response rate at 8 cycles		
ORR (CR+PR)	38 (52)	76 (52)
p-value[a]	0.0001	
CR n (%)	9 (12)	15 (10)
PR n (%)	29 (40)	61 (42)
nCR n (%)	7 (10)	14 (10)
Intent to treat population[b]	**n = 74**	**n = 148**
TTP, months	9.4	10.4
(95% CI)	(7.6, 10.6)	(8.5, 11.7)
Hazard ratio (95% CI)[c]	0.839 (0.564, 1.249)	
p-value[d]	0.38657	
Progression free survival, months	8.0	10.2
(95% CI)	(6.7, 9.8)	(8.1, 10.8)
Hazard ratio (95% CI)[c]	0.824 (0.574, 1.183)	
p-value[d]	0.295	
Progression free survival, months	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 21 presents a cross-tabulation summary of best response by algorithm after 4 cycles versus after 8 cycles for patients who received dexamethasone. Eighty-two subjects in the SC treatment group and 39 subjects in the IV treatment group received dexamethasone after cycle 4.

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

- 30% (SC) and 30% (IV) of patients with no response at end of cycle 4 obtained a response later in subsequent cycles (cycle 5 through 8).
- 13% (SC) and 13% (IV) of patients with PR at end of cycle 4 obtained a CR later in subsequent cycles (cycle 5 through 8).

Table 21: Cross-tabulation of summary of best response after 4 cycles vs after 8 cycles for patients who received dexamethasone

	Best response after 8 cycles (n = 121)			
Treatment group	**Total**	**Category, n (%)**		
Cycle 4 best response*	**n (%)**	**CR**	**PR**	**Non-responder**
IV	39 (32)	3 (8)	20 (51)	16 (41)
CR	1 (1)	1 (100)	0	0
PR	15 (12)	2 (13)	13 (87)	0
Non-responder	23 (19)	0	7 (30)	16 (70)
SC	82 (68)	8 (10)	41 (50)	33 (40)
CR	4 (3)	4 (100)	0	0
PR	31 (26)	4 (13)	27 (87)	0
Non-responder	47 (39)	0	(30)	33 (70)

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

Relative to previously reported outcomes, the ORR after 8 cycles of treatment (52% in both treatment groups) and time to progression (median 10.4 months and 9.4 months in SC and IV treatment groups, respectively), including the effect of the addition of dexamethasone from cycle 5 onwards, were higher than observed in prior registration study with single agent IV bortezomib (38% ORR and median TTP of 6.2 months for the bortezomib arm). Time to progression and ORR was also higher compared to the subgroup of patients on APEX that received only 1 prior line of therapy (43% ORR and median TTP of 7.0 months) .

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

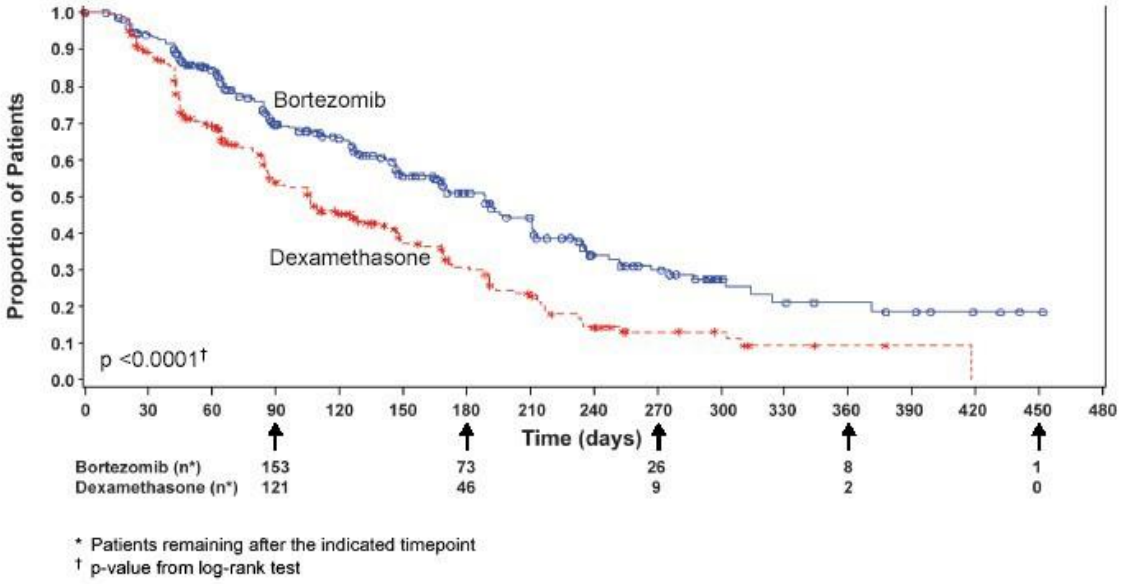


Figure 3: Time to progression bortezomib vs dexamethasone

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

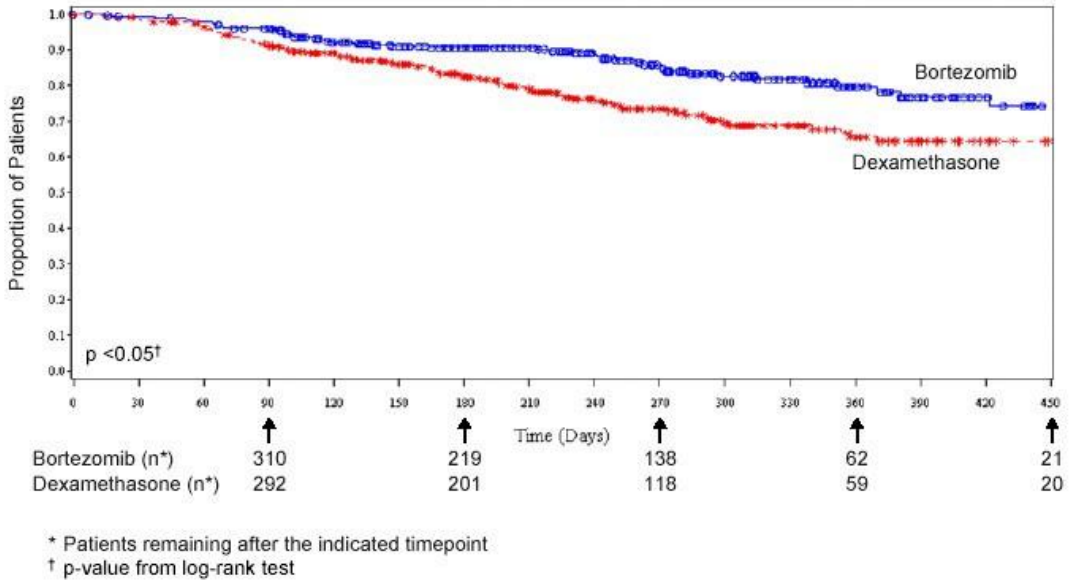


Figure 4: Overall survival bortezomib vs dexamethasone

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, 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, multicenter 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 Adverse effects (Undesirable effects)**).

Phase 2 clinical studies in relapsed multiple myeloma

The safety and efficacy of bortezomib were evaluated in an open-label, single-arm, multi-centre study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Dosing regimens and baseline patient and disease characteristics are summarised in previous tables. 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 Dose and method of administration**).Patients who experienced a response to bortezomib were allowed to continue bortezomib treatment in an extension study.

Responses to bortezomib alone in the Phase 2 study are shown in **Table 2 2**. 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 nonmeasurable disease could not be evaluated for response by the IRC, and 5 patients were excluded from the efficacy analyses because they had 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 confirmed complete response 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 – 127 days). The median survival of all patients enrolled was 16 months (range < 1 to 18+ months). The response rate to bortezomib was independent of the number and types of prior therapies.

Table 22: Summary of disease outcomes in 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)[1]	5 (2.7%)	(1,6)
Partial response (PR)[2]	47 (25%)	(19, 32)
Clinical remission (SWOG)[3]	33 (17.6%)	(12, 24)
Kaplan-Meier estimated median duration of response (95% CI)	365 Days	(224, NE)

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

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

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

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.

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.

Relapsed mantle cell lymphoma

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, multicenter 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 23**.

Table 23: 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

Study LYM-3002 was a Phase 3, randomised, open-label study comparing the efficacy and safety of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP; n = 243) which resulted in improvement in progression free survival (PFS), when compared to that the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n = 244) in adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV). Patients of median age 66 years enrolled in this trial were either ineligible (e.g. due to age or comorbidity; n = 407) or were not considered (e.g. due to transplant unavailability, financial unaffordability or patient refusal, despite being medically eligible; n = 80) for stem-cell transplantation. This clinical study utilized independent pathology confirmation and independent radiologic response assessment.

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

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).

The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 66% were Caucasian and 32% Asian, 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of ≥ 3, and 74% had Stage IV disease. Treatment duration (median = 17 weeks) and duration of follow-up (median = 40 months) were comparable in both treatment arms. A median of 6 cycles was received by patients in both treatment arms with 14% of subjects in the VcR-CAP group and 17% of patients in the R-CHOP group receiving 2 additional cycles. The majority of the patients in both groups received 6 or more cycles of treatment, 83% in the R-CHOP group and 84% in the VcR-CAP group.

A statistically significant benefit in favour of the VcR-CAP treatment group was observed for the median values for PFS, TTP, TNT, TFI and overall survival, over the entire duration of the study.

At a median follow up of 40 months, a 59 % improvement in the primary endpoint of PFS [hazard ratio (HR) 0.63, 95 % CI 0.50 – 0.79; p = 0.001] was observed in the VcR-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 VcR-CAP group (42.1 months) compared with the R-CHOP group (18 months) and the duration of overall response was 21.4 months longer in the VcR-CAP group.

At a median follow-up of 40 months, median OS (56.3 months in the R-CHOP group, and not reached

in the VcR CAP group) favoured the VcR-CAP group, (estimated HR = 0.80; *p* = 0.173). There was a trend towards prolonged overall survival favouring the VcR-CAP group; at this point in time, with the estimated 4-year survival rate was 53.9% in the R-CHOP group and 64.4% in the VcR-CAP group.

Overall survival demonstrated statistical significance in the final analysis, after a median follow-up of 82 months. Median OS in the VcR-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 24**.

Table 24: Summary of efficacy outcomes in a Phase 3 mantle cell lymphoma study in previously untreated patients (LYM-3002)

Efficacy endpoint	VcR-CAP n = 243 (ITT patients)	R-CHOP n = 244 (ITT patients)	
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)	
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			
n: ITT patients	243	244	
Events n (%)	71 (29.2%)	87 (35.7 %)	HR[d] (95% CI) = 0.80 (0.59; 1.10) *p*-value[e] < 0.173
Median[c] (95% CI) (months)	NE (56.0; NE)	56.3 (47.2; NE)	
4-year survival rate % (95% CI)	64.4 (56.4, 71.4)	53.9 (45.2; 61.9)	
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) = 1.688 (1.148; 2.481)

			p-value[g] = 0.007
Response duration			
Duration of complete response (CR+CRu)[j]			
n: response-evaluable patients	122	95	
Median[c] (95% Cl) (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% Cl) (months)	36.5 (26.7; 46.7)	15.1 (12.5; 17.0)	

[a] Based on IRC assessment (radiological data only).
[b] Based on Investigator assessment.
[c] Based on Kaplan-Meier product limit estimates.
[d] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.
[e] Based on Log rank test stratified with IPI risk and stage of disease.
[f] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and Stage of Disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.
[g] P-value from the Cochran Mantel-Haenszel Chi-Squared test, with IPI and Stage of Disease as stratification factors.
[h] Include all CR + CRu, by IRC, bone marrow and LDH.
[i] Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.
[j] Calculated from first date of complete response (CR+CRu by IRC, bone marrow and LDH) to date of PD or death due to PD.
[k] Calculated from first date of response (include all radiological CR+CRu+PR by IRC) to date of PD or death due to PD.
IRC = Independent Review Committee; IPI = International Prognostic Index; LDH = Lactate dehydrogenase; CR = Complete response; CRu = Complete response unconfirmed; PR = Partial response; CI = Confidence interval, HR = hazard ratio; OR = odds ratio; ITT = intent to treat; PD = Progressive disease

Pediatric use

The safety and effectiveness of bortezomib in pediatric patients has not been established for multiple myeloma and mantle cell lymphoma.

Geriatric use

Of the 669 patients enrolled in the Phase 3 multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the bortezomib arm and 120 (36%) on dexamethasone arm. Median time to progression and median duration of response for patients ≥ 65 were longer on bortezomib compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively]. On the bortezomib arm, 40% (n = 46) of evaluable patients aged ≥ 65 experienced response (CR+PR) versus 18% (n = 21) on the dexamethasone arm. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for bortezomib patients ≤ 50, 51 – 64 and ≥ 65 years old, respectively (see **Section 5.1 Pharmacodynamic properties, Clinical trials**).

In the Phase 2 clinical study of 202 patients with relapsed multiple myeloma, 35% of patients were 65 years of age or older, the incidence of Grade ≥ 3 events was 74%, 80%, and 85% for bortezomib patients ≤ 50, 51 – 65, and > 65 years old, respectively (see **Section 5.1 Pharmacodynamic properties, Clinical trials**).

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

5.2. PHARMACOKINETIC PROPERTIES

Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to eleven patients with multiple myeloma, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 – 106 ng/mL for the 1.0 mg/m^2 dose and 89 – 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 – 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 1,659 – 3,294 litres (489 – 1,884 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 – 1,000 ng/mL, the *in vitro* protein binding averaged 83% in human plasma. The percent of bortezomib bound to plasma proteins was not concentration dependent.

Metabolism

Bortezomib is metabolised by the liver enzymes. *In vitro* studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, 2D6, 2C9, and 1A2. 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.

Excretion

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

Special populations

Age, gender and race

Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 (25%) L/hr/m^2, volume of distribution at steady-state was 834 (39%) L/m^2, and the elimination half-life was 100 (44%) hours.

After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalised clearance of bortezomib in pediatric patients was similar to that observed in adults.

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

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 – 1.3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C_{max}) was comparable among all the groups (see **Section 4.4 Special warnings and precautions for use**).

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of IV bortezomib was assessed in 60 cancer patients at bortezomib doses ranging from 0.5 – 1.3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalised bortezomib AUC. However, the dose-normalised mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely (see **Table 5**).

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

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

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

Carcinogenicity

Carcinogenicity studies have not been conducted with bortezomib.

Animal toxicity findings

Cardiovascular toxicity

Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension,

bradycardia, and death 12 – 14 hours post dose. Doses ≥ 1.2 mg/m^2 induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Chronic administration

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

Impairment of fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Mannitol
Nitrogen

6.2. INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in **Section 4.2 Dose and method of administration**.

6.3. SHELF LIFE

Unopened vials: refer to outer carton for shelf life.

Reconstituted solution: 8 hours when stored between 2 – 8 °C (see **Section 6.4 Special precautions for storage**)

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.

Reconstituted solution:

BORTEZOMIB-AFT 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. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. If storage is necessary, hold at 2-8°C for up to 8 hours.

Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER

BORTEZOMIB-AFT is supplied in a 10 mL glass vial with bromo- butyl rubber stopper and aluminium cap.
BORTEZOMIB-AFT is available in cartons containing 1 vial. Product is for single use in one patient only.
The vial does not include an overfill.

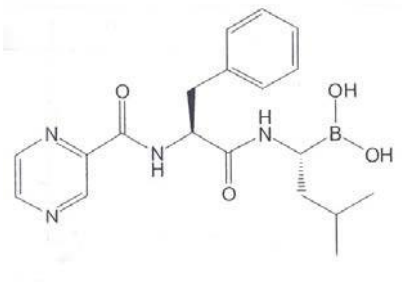
6.6. SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL

See **Section 4.2 Dose and method of administration, Instructions for use and handling and disposal**.

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

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS number: 179324-69-7

7. FORENSIC CLASSIFICATION

Prescription Only Medicine

8. PRODUCT OWNER

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Product registration number: SIN 16586P

9. DATE OF FIRST APPROVAL

1 September 2022

10. DATE OF REVISION

Not applicable.