Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Bortezomib

## Proprietary Product Name: Velcade

## Sponsor: Janssen-Cilag Pty Ltd

**November 2011**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# I. Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | Extension of Indications |
| *Decision:* | Approved |
| *Date of Decision:* | 27 October 2011 |
| | |
| *Active ingredient(s):* | Bortezomib |
| *Product Name(s):* | Velcade |
| *Sponsor's Name and Address:* | Janssen-Cilag Pty Ltd |
| | 1-5 Khartoum Rd. Macquarie Park NSW 2113 |
| *Dose form(s):* | Powder for Injection |
| *Strength(s):* | 3.5 mg and 1mg. |
| *Container(s):* | Glass vial |
| *Pack size(s):* | 1's |
| *Approved Therapeutic use:* | *Velcade, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.* [1] |
| *Route(s) of administration:* | Intravenous (IV) |
| *Dosage:* | As per Product Information (PI) in Attachment 1. |
| *ARTG Number (s)* | 148329 and 104542 |

## Product Background

Bortezomib is an anticancer agent which acts through inhibition of the proteasome, an intracellular protein complex which is responsible for the degradation of cellular proteins. Inhibition of the proteasome results in decreased degradation of Iκ-B, an inhibitory protein. Iκ-B inhibits the actions of nuclear factor-κB (NF-κB), a transcription factor which promotes cell proliferation and blocks cell death pathways.

[1] The full indications for Velcade are now:

- Velcade, in combination with melphalan and prednisone, is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy.
- Velcade, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.
- Velcade is also indicated for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.

The drug was initially registered in 2006 following consideration by Australian Drug Evaluation Committee (ADEC, now called Advisory Committee on Prescription Medicines or ACPM) at its December 2005 meeting. The sponsor sought, and was granted, **a second-line indication.** The approved wording was as follows:

> *".. for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease."*

In 2008, the sponsor sought to extend the approved indications to include **first-line treatment** of myeloma, as part of combination therapy. The only Phase III data submitted with the application were from the VISTA trial comparing the combination of bortezomib plus melphalan and prednisone (VcMP) versus melphalan and prednisone (MP) alone, in patients who were not considered eligible for high dose chemotherapy (HDC) with stem cell rescue. There were no Phase III data of use of the drug in combination with other agents or as part of combination therapy in patients undergoing HDC. Therefore, the first-line indication that was approved was restricted as follows:

> *".. in combination with melphalan and prednisone ... for the treatment of patients with previously untreated myeloma who are not suitable for high dose chemotherapy."*

The current Australian application seeks approval for a broad first line indication that encompasses use in patients eligible or ineligible for HDC and with no restriction on the agents it can be combined with. The proposed wording is:

> *".. as part of combination therapy ... for the treatment of patients with previously untreated multiple myeloma."*

At the time of ADEC consideration of the first line application (December 2008), it was noted that there were several ongoing Phase III trials of bortezomib (in combination with other agents) as induction therapy in patients eligible for HDC. The current application is based on the results of some of these studies. The application is literature based, as the Phase III trials conducted in the setting of patients eligible for HDC have all been conducted by independent investigators.

This AusPAR describes the literature based submission made by the sponsor to extend the indication of Velcade (bortezomib) 3.5 mg and 1mg powder for injection as indicated above.

## Regulatory Status

A summary of the current regulatory status of Velcade is provided in Table 1 below.

**Table 1. Summary of international regulatory status.**

| Country | Indication | Application approval date | Comments |
|---|---|---|---|
| **Canada** | FL | 2 September 2008 | |
| | 2nd line | 24 April 2006 | |
| | 3rd line | 27 January 2005 | |
| | MCL | 9 June 2008 | |
| **Germany** | FL | 2 September 2008 | |
| | 2nd line | 20 April 2005 | |
| | 3rd line | 1 May 2004 | |
| | 1 mg | 21 April 2008 | |
| **New Zealand** | FL | 2 June 2009 | |
| | 3rd line | 20 October 2005 | |
| | 1 mg | 9 November 2009 | |
| **Sweden** | FL | 29 August 2008 | |
| | 2nd line | 20 April 2005 | |
| | 3rd line | 26 April 2004 | |
| | 1 mg | 21 April 2008 | |
| **Switzerland** | FL | 12 December 2008 | |
| | 2nd line | 1 March 2006 | |
| | 3rd line | 26 January 2005 | |
| | MCL | 6 May 2009 | |
| | 1 mg | 15 August 2008 | |
| **United Kingdom** | FL | 2 September 2008 | 1 mg N L |
| | 2nd line | 20 April 2005 | |
| | 3rd line | 26 April 2004 | |
| | 1 mg | 21 April 2008 | |
| **United States** | FL | 26 June 2008 | |
| | 2nd line | 25 March 2005 | |
| | 3rd line | 13 May 2003 | |
| | MCL | 8 December 2006 | |

NL=Market authorisation approved but not launched. FL= follicular lymphoma, MCL= mantle cell lymphoma

## Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality Findings

There was no requirement for a quality evaluation in a submission of this type.

# III. Nonclinical Findings

There was no requirement for a nonclinical evaluation in a submission of this type.

# IV. Clinical Findings

## Introduction

On the basis of Study MM-3002 (VISTA study) of 682 patients (median age 71 years), Velcade was approved in January 2009 for use in combination with melphalan and prednisone for patients with previously untreated multiple myeloma (MM), who were not eligible for high dose chemotherapy and stem cell transplant.

The sponsor has now provided data in support of the application for the use of bortezomib in patients with newly diagnosed MM who are candidates for high dose chemotherapy and autologous stem cell transplantation.

The current Australian literature based submission was supported by four Phase III studies. Two of these studies, GIMMEMA[2] and IFM 2005[3], have been published. The other two studies, HOVON and PETHEMA, have not been published and only the abstracts were provided. The sponsor also provided the study protocols for all four studies. The clinical evaluator proposed to examine GIMMEMA as the pivotal study, and IFN 2005 and the other two Phase III studies as supportive studies. The sponsor has also provided various Phase I/II studies in tabular form from the literature in support of the submission.

## Efficacy

### Pivotal Efficacy Studies

#### *GIMEMA STUDY: Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem cell transplantation in newly diagnosed multiple myeloma: A randomised Phase 3 study.*

This is a prospective, open label, randomised (1:1) clinical study of treatment with thalidomide plus dexamethasone alone or with bortezomib (Velcade), of patients aged 18-65 years who are candidates to receive double autologous transfusion for previously untreated symptomatic myeloma. The study was conducted at 73 hospitals in the GIMEMA Myeloma network in Italy between May 2006 and April 2008. Data collection continued until 30 June 2010. The study is continuing but is not recruiting participants.

[2] Cavo M *et al* (2010). Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *The Lancet* 376:2075-2085.

[3] Harousseau J-L *et al* (2010). Bortezomib Plus Dexamethasone Is Superior to Vincristine Plus Doxorubicin Plus Dexamethasone As Induction Treatment Prior to Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: Results of the IFM 2005-01 Phase III Trial. *J Clin Oncol* 28:1-10.

The primary objective of the study was to compare the rate of response of the two treatment regimens administered as primary therapy in preparation for autologous peripheral blood stem cells (PBSC) transplantation for previously untreated symptomatic multiple myeloma.

The secondary objectives included the comparison of the rate of response to either Velcade+Thalidomide+Dexamethasone (VcTD) or Thalidomide+Dexamethasone (TD) administered as consolidation therapy; the Time-To-Progression (TTP), Overall Survival (OS) and Event Free Survival (EFS) to either VcTD or TD administered as primary therapy before and as consolidation therapy following autologous PBSC transplantation; the comparison of toxicities between the two groups of patients treated with either VcTD or TD in this study.

The primary study endpoint was the rate of ≥ near complete remission (nCR) after induction therapy with VcTD or TD as determined by European Group for Blood and Marrow Transplantation (EBMT/IBMTR) criteria[4] and calculated on an intention-to-treat basis. The secondary endpoints included rate of ≥ nCR (by EBMT/IBMTR criteria and calculated on an intent-to-treat basis) after consolidation therapy; TTP, OS, and EFS in the two groups; and safety and toxicities, both haematologic and non haematologic.

*Inclusion and exclusion criteria*

The inclusion criteria included patients 18-65 years with a confirmed diagnosis of multiple myeloma with a Karnofsky performance status (PS) ≥ 60%[5]. The exclusion criteria included previous treatment for multiple myeloma, history of thromboembolic disease and presence of ≥ Grade 2 peripheral neuropathy. A patient is discontinued from the study if there is disease progression or failure to qualify for at least a single autologous transfusion.

[4]Bladé J *et al (*1998). Criteria for Evaluating Disease Response and Progression in Patients with Multiple Myeloma Treated by High-Dose Therapy and Haemopoietic Stem Cell Transplantation. *Brit J Haematol* 102:1115-1123.

[5] Karnofsky Performance Status

| Points | Description |
|---|---|
| 100 | Normal, no complaints, no evidence of disease |
| 90 | Able to carry on normal activity |
| 80 | Normal activity with effort; some signs or symptoms of disease |
| 70 | Cares for self unable to carry on normal activity or to do active work |
| 60 | Required occasional assistance but is able to care for most of his/her needs |
| 50 | Required considerable assistance and frequent medical care |
| 40 | Disabled; required special care and assistance |
| 30 | Severely disabled; hospitalization indicated. Death not imminent |
| 20 | Very sick; hospitalization necessary; active support treatment necessary |
| 10 | Moribund; fatal processes progressing rapidly |
| 0 | Dead |

*Discontinuation of Treatment*

A subject should be discontinued from treatment if:

- he/she has disease progression, as defined by EBMT/IBMTR criteria;
- he/she has failed to collect the minimum threshold dose of CD34+ cells to receive at least a single autologous transplantation ($\geq 2.0 \times 10^6$ CD34+ cells/kg);
- the investigator believes that for safety reasons (e.g., adverse event) it is in the best interest of the subject to stop treatment;
- the subject becomes pregnant;
- patient request.

*Study treatments*

The patients were randomised (1:1) to either Treatment arm A (VcTD) or treatment arm B (TD) using a web-based system at the coordinating centre in Bologna, Italy**.** The study design is described in Figures 1 and 2 below.

**Figure 1. Study design.**

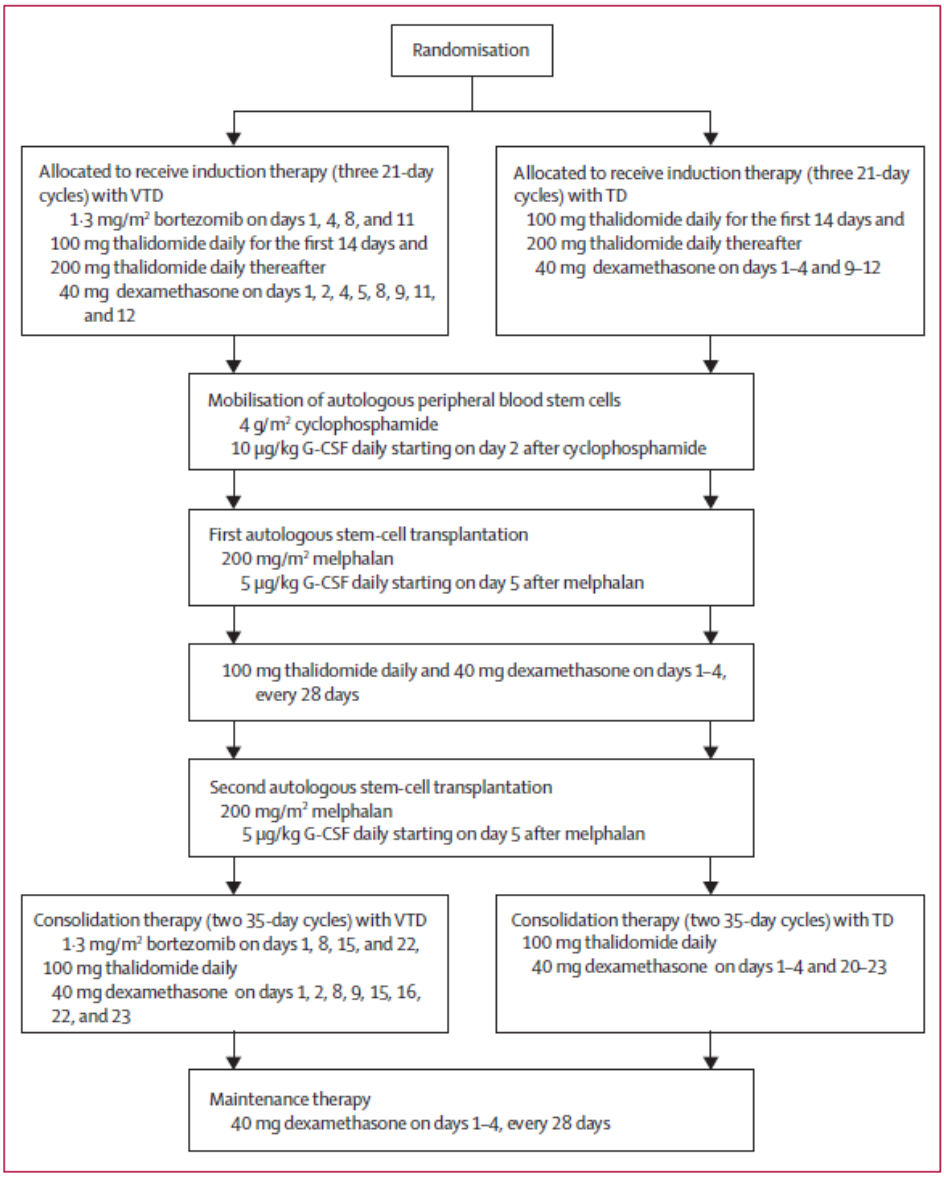
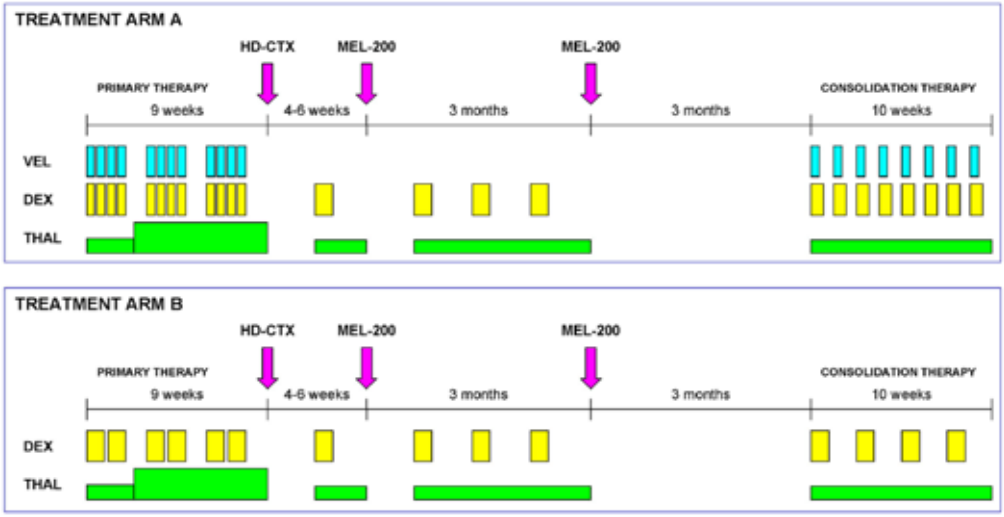



***Figure 1:*** **Trial design**
VTD=bortezomib with thalidomide plus dexamethasone. TD=thalidomide plus dexamethasone.
G-CSF=granulocyte colony-stimulating factor.

**Figure 2. Treatment Phase and Study Duration.**




In each arm, the patients received 9 weeks of induction therapy. This was followed by collection of peripheral blood stem cells (PBSC) with high dose cyclophosphamide (HD-CTX) support in both study arms. Both treatment arms then received daily thalidomide and pulsed courses of dexamethasone, starting the day after the last harvest of PBSC and continued until the first course of high dose melphalan (MEL). After the first transplantation and after recovery of haematopoiesis (absolute neutrophil count (ANC) >1x$10^9$/L and platelet count (PLT) > 75x$10^9$/L), the thalidomide and dexamethasone treatment is resumed until the day before the second course of MEL, for the second course of PBSC. After the autologous transplant, the patients in arms A and B receive 10 weeks of consolidation therapy with VcTD or TD, respectively, followed by maintenance therapy with monthly dexamethasone.

Patients who receive an allogenic transplant (recommended for patients at high risk; such as those with cytogenetic abnormalities, t4;14[6]) receive only the induction therapy but not consolidation therapy.

If haematological toxicity occurs, Velcade dose modification or delay is warranted until ANC is ≥1x$10^9$/L and PLT ≥ 75x$10^9$/L. Velcade and Thalidomide dose delay or modification is warranted if the patient experiences Grade 3 neutropaenia or a platelet count ≤ 10,000 cells/μL.

The drugs are ceased until the platelet count is ≥ 30,000 cells/μL and ANC ≥ 750 cells/μL. If recovery does not occur, the study drugs are discontinued. If the patient experiences any Grade ≥ 3 non-haematological toxicity, Velcade and Thalidomide are ceased until the toxicity returns to ≤ Grade 2. The study drugs are discontinued if the recovery does not occur. If neuropathic pain or peripheral sensory neuropathy were to occur, the action for Velcade varies from no action, to dose reduction, to discontinuation. See Table 2 below for details. The action taken for Thalidomide induced > Grade 3 neuropathic pain or peripheral sensory neuropathy is cessation of the drug until toxicity returns to Grade 2 or better and then restarting the drug at 50% of the original dose.

[6] The t(4;14) abnormality is a translocation of a region of chromosome 4 to chromosome 14. This abnormality is associated with poor overall survival in myeloma patients.

Concomitant therapy that is permitted includes bisphophonates, Granulocyte Colony Stimulating Factors, Recombinant Human Erythropoietin, platelet transfusions, antimicrobial and antiviral drugs (Aciclovir prophylaxis for patients receiving VcTD), constipation prophylaxis, loperamide, antiemetics and anticoagulants.

The protocol for a substudy to determine the optimal prophylaxis against thalidomide related deep vein thrombosis (DVT) was described but the results of the study were not available. Thrombosis prophylaxis will not be discussed further.

**Table 2. Velcade Dose Modifications for Peripheral Sensory Neuropathy**

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

ADL = activities of daily living
Hold = Interrupt VELCADE for up to 3 weeks until the toxicity returns to Grade 1 or better.
Schedule Δ Required = Schedule change from VELCADE twice weekly (Days 1, 4, 8, 11) to once weekly (Days 1, 8) required. If the subject is already on a once weekly schedule, then VELCADE will be given every other week (i.e., Day 1, Day 22).
For subjects previously treated with 1.3 mg/m$^2$ of VELCADE, "reduction by 1 dose level" means reduction to 1.0 mg/m$^2$ of VELCADE, and "reduction by 2 dose levels" means reduction to 0.7 mg/m$^2$ of VELCADE (+ schedule Δ if indicated by the table). For subjects previously treated with 1.0 mg/m$^2$ of VELCADE, "reduction by 1 dose level" means reduction to 0.7 mg/m$^2$ of VELCADE; in case of "reduction by 2 dose levels" a reduction to 0.7 mg/m$^2$ of VELCADE always combined with a schedule Δ should be applied. For subjects previously treated with 0.7 mg/m$^2$ of VELCADE, in case of "reduction by 1 dose level" and "reduction by 2 dose levels" a schedule Δ should be applied.

The study schedule included a pre randomisation phase, primary remission induction therapy, the collection of PBSC, first autologous transplantation, second autologous transplantation, remission consolidation therapy and maintenance therapy.

*Efficacy variables and outcomes*

The main efficacy variables were:

- Myeloma protein in blood and urine
- Bone marrow cytogenetics and molecular biology following bone marrow biopsy.
- Skeletal survey: a complete bone survey, including humeri and femora, is performed by magnetic resonance imaging (MRI) and, if possible, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) imaging.
- Extramedullary plasmacytomas by clinical and radiological means (MRI and/or 18F-FDG PET/CT)

The primary efficacy outcome was the rate of ≥ nCR after induction therapy with VcTD or TD as determined by EBMT/IBMTR criteria and calculated on an intent-to-treat basis.

Other efficacy outcomes included the rate of ≥ nCR (by EBMT/IBMTR criteria and calculated on an intent-to-treat basis) after consolidation therapy, and TTP, OS and EFS in the two groups.

The evaluation of outcomes is according to EBMT criteria. Patients with 'Complete response' who lacked confirmation from bone marrow biopsy were downgraded to 'very good partial response' (VGPR).

### *Sample size*

The study was planned to have 80% power to detect a significant difference (p=0.05, two sided) in treatment effect corresponding to an improvement in ≥ nCR from 15% with TD to 27% with VcTD, as primary remission induction therapy prior to autologous PBSC transplant. The required sample size was 180 patients in each arm. It was planned to enrol 225 patients per arm on the basis of an 80% retention rate. Assuming an accrual rate of 120 patients per year, the study was expected to have duration of 4 years.

*Randomisation and blinding methods*

Randomization was based on a computer generated randomisation schedule, prepared by the Coordinating Centre, before the study. The patients randomised to treatment arm A received VcTD and those randomised to treatment arm B received TD. The patients and treating staff were not blinded to treatment allocation.

*Statistical methods*

The study populations are the intent to treat (ITT) population which include all the patients who were randomised. The treated population (TP) includes all those who received at least one dose of treatment.

Efficacy analyses include comparison of rate of response (≥ nCR) to primary therapy (primary efficacy analysis) and to consolidation therapy (secondary efficacy analysis) with either VcTD or TD. Comparison of the response rates between the 2 groups is performed using Fisher's exact test and the 95% confidence interval provided.

The other secondary endpoints include time-to-progression (TTP; time from start of treatment to the date of first recorded evidence of progression or relapse), overall survival (OS; the time from start of treatment to death or last follow up), and event free survival (EFS; time from start of treatment to either death or progression/relapse). TTP, OS and EFS will be compared between the two groups using the log rank test and the Kaplan-Meier method will be used to estimate the distribution of TTP, OS and EFS for each group. Comparison of time to first response (time from start of treatment to first evidence of a confirmed response) and duration of response (time from achievement of response to progression or relapse) between the two groups will be performed.

Safety analyses, both haematological and non-haematological, include adverse events, vital signs, laboratory tests and ECOG performance status scores[7]. All adverse events and serious adverse events that occur from start of study to 30 days after the last dose will be reported. All Grade 3 and 4 events that are considered related must be followed until resolution of the event or improvement to Grade 2.

*Participant flow*

In all 508 patients were assessed for eligibility and 480 were enrolled and randomly assigned. Of these 6 patients withdrew consent, leaving 236 patients to receive VcTD, and 238 to receive TD. There were more discontinuations in the TD arm, noticeably for disease progression, than in the VcTD arm. Toxic effects accounted for more discontinuations in the VcTD arm than in the TD arm. Some 130 patients in the VcTD arm and 114 patients in the TD arm remained and were on maintenance therapy. Median follow up was 36 months from the start of study treatment.

*Baseline data*

Demographic and disease characteristics were well balanced between treatment groups at baseline. Data on cytogenetic abnormalities, detected by FISH (fluorescence *in-situ* hybridisation) analysis was available in > 90% of the patients. Patients with these abnormalities were equally distributed in the two groups.

*Results for the primary efficacy outcome*

The rates for complete response (CR), near complete response (nCR) and very good partial response (VGPR) were significantly better in the VcTD arm than in the TD arm. A CR was achieved by 44 patients (19%) in the VcTD arm and by 11 patients (5%) in the TD arm. A ≥ nCR was achieved by 73 (31%) patients in the VcTD arm and by 27 (11%) patients in the TD arm. The rates for ≥ VGPR were 62% (146 patients) in the VcTD arm versus 28% (66 patients) in the TD arm (see Table 3 below).

[7] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 – Dead

**Table 3. Reponse to different treatment phases and best response, according to central assessment**

| | VTD (n=236) | TD (n=238) | p value |
|---|---|---|---|
| **After induction therapy** | | | |
| Complete response | 44 (19%, 13·7–23·6) | 11 (5%, 2·0–7·3) | <0·0001 |
| Complete or near complete response*† | 73 (31%, 25·0–36·8) | 27 (11%, 7·3–15·4) | <0·0001 |
| Very good partial response or better | 146 (62%, 55·7–68·1) | 66 (28%, 22·0–33·4) | <0·0001 |
| Partial response or better | 220 (93%, 90·0–96·4) | 187 (79%, 73·4–83·8) | <0·0001 |
| Minimal response or stable disease | 16 (7%, 3·6–10·0) | 39 (16%, 11·7–21·1) | 0·0011 |
| Progressive disease | 0 | 12 (5%, 2·3–7·8) | 0·0005 |
| **After first autologous stem-cell transplantation** | | | |
| Complete response | 89 (38%, 31·5–43·9) | 54 (23%, 17·4–28·0) | 0·0004 |
| Complete or near complete response* | 123 (52%, 45·7–58·5) | 74 (31%, 25·2–37·0) | <0·0001 |
| Very good partial response or better | 186 (79%, 73·6–84·0) | 137 (58%, 51·3–63·8) | <0·0001 |
| Partial response or better | 220 (93%, 90·0–96·4) | 201 (84%, 79·9–89·1) | 0·0025 |
| Minimal response or stable disease | 15 (6%, 3·2–9·5) | 20 (8%, 4·9–11·9) | 0·39 |
| Progressive disease | 1 (<1%, 0·0–1·3) | 17 (7%, 3·9–10·4) | 0·0001 |
| **After second autologous stem-cell transplantation** | | | |
| Complete response | 98 (42%, 35·2–47·8) | 72 (30%, 24·4–36·1) | 0·0105 |
| Complete or near complete response* | 130 (55%, 48·7–61·4) | 98 (41%, 34·9–47·4) | 0·0024 |
| Very good partial response or better | 193 (82%, 76·9–86·7) | 152 (64%, 57·8–70·0) | <0·0001 |
| Partial response or better | 220 (93%, 90·0–96·4) | 199 (84%, 78·9–88·3) | 0·0011 |
| Minimal response or stable disease | 14 (6%, 2·9–8·9) | 19 (8%, 4·5–11·4) | 0·38 |
| Progressive disease | 2 (1%, 0·0–2·0) | 20 (8%, 4·9–11·9) | 0·0001 |
| **After consolidation therapy** | | | |
| Complete response | 116 (49%, 42·8–55·5) | 82 (34%, 28·4–40·5) | 0·0012 |
| Complete or near complete response* | 147 (62%, 56·1–68·5) | 108 (45%, 39·1–51·7) | 0·0002 |
| Very good partial response or better | 201 (85%, 80·6–89·7) | 162 (68%, 62·1–74·0) | <0·0001 |
| Partial response or better | 218 (92%, 89·0–95·8) | 201 (84%, 79·9–89·1) | 0·0071 |
| Minimal response or stable disease | 12 (5%, 2·3–7·9) | 16 (7%, 3·5–9·9) | 0·45 |
| Progressive disease | 6 (3%, 0·5–4·6) | 21 (9%, 5·2–12·4) | 0·0032 |
| **Best response to overall treatment protocol** | | | |
| Complete response | 136 (58%, 51·3–63·9) | 97 (41%, 34·5–47·0) | 0·0001 |
| Complete or near complete response | 168 (71%, 65·4–77·0) | 128 (54%, 47·4–60·1) | <0·0001 |
| Very good partial response or better | 210 (89%, 85·0–93·0) | 175 (74%, 67·9–79·1) | <0·0001 |
| Partial response or better | 227 (96%, 93·7–98·6) | 212 (89%, 85·1–93·0) | 0·0031 |
| Minimal response, stable disease, or progressive disease | 9 (4%, 1·4–6·3) | 26 (11%, 7·0–14·9) | 0·0031 |

Data are number (%, 95% CI). VTD=bortezomib with thalidomide plus dexamethasone. TD=thalidomide plus dexamethasone. *Study investigators reported similar differences in response rates between treatment groups after induction therapy (n=76, 32% vs n=32, 13%; p<0·0001), and after transplantation and consolidation (data not shown) to those centrally assessed. †The significant difference between treatment groups was maintained after use of cyclophosphamide to mobilise peripheral blood stem cells (n=100, 42% vs n=51, 21%; p<0·0001).

*Results for other efficacy outcomes*

The rates of CR, nCR and VGPR were significantly higher in the VcTD arm than in the TD arm after the first and second autologous transplantations and the subsequent consolidation therapy.

A post hoc comparative analysis of the CR, nCR and VGPR rates for the full treatment protocol in the VcTD and TD arms was made using the chi squared test. The rates were significantly higher in the VcTD arm than in the TD arm (see Table 3).

The median time to best complete or near complete response was significantly shorter in the VcTD arm (9 months) than in the TD arm (14 months) by Kaplan-Meier analysis with a HR of 0.61 (95% CI 0.49-0.76; p<0.0001) (see Figure 3 A).

The estimated 3 year probability of progression or relapse was 29% in the VcTD arm and 39% in the TD arm (p=0.0061) by Kaplan-Meier analysis with a HR of 0.61 (95% CI 0.43-0.87; p=0.0073) (see Figure 3 B).

Progression free survival (PFS) was significantly longer in the VcTD arm than in the TD arm (HR 0.63, 95% CI 0.45-0.88; p=0.0061). The estimated 3 year rate of progression free survival was 68% in the VcTD arm and 56% in the TD arm (p=0.0057) by Kaplan-Meier analysis (see Figure 3 C).

Some 58 patients (25%) in the VcTD arm and 86 patients (36%) in the TD arm progressed or died during the study. The estimated 3-year rate of overall survival was 86% in the VcTD arm and 84% in the TD arm (p=0.30) by Kaplan-Meier analysis.

**Figure 3. Kaplan-Meier curves for (A) time to best complete or near complete response, (B) time to progression or relapse, and (C) progression free survival**

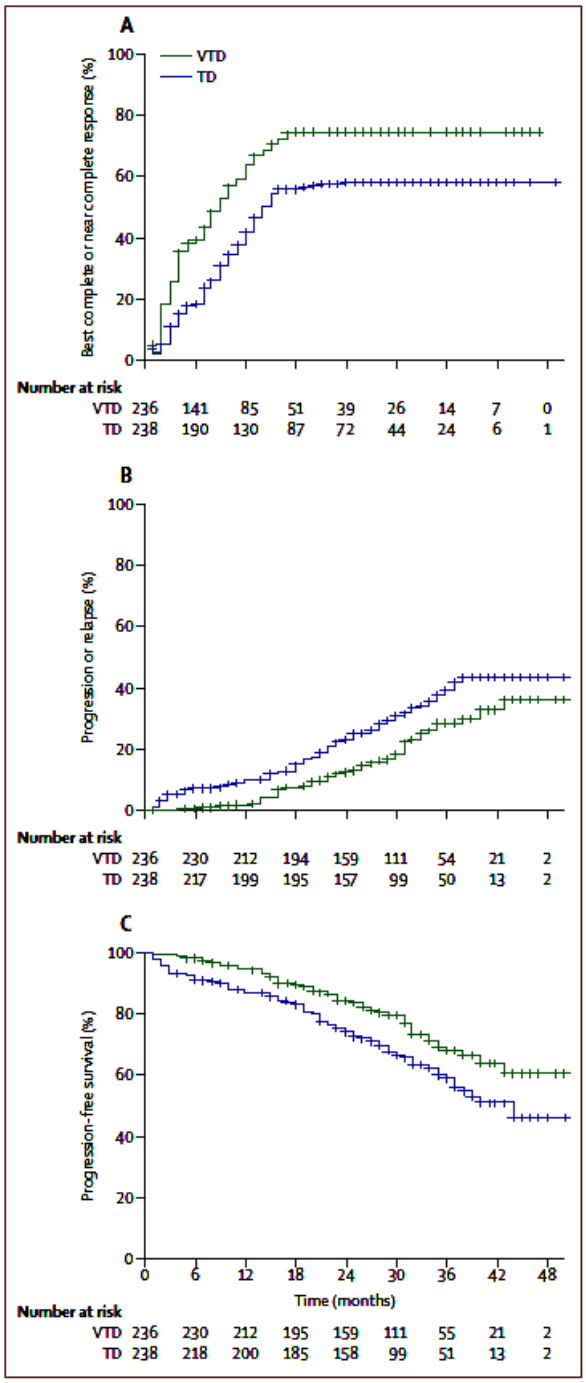



*Figure 3:* **Kaplan-Meier curves for (A) time to best complete or near complete response, (B) time to progression or relapse, and (C) progression-free survival**
VTD=bortezomib with thalidomide plus dexamethasone. TD=thalidomide plus dexamethasone.

Rates of CR, nCR and PFS were higher in the VcTD arm than in the TD arm across subgroups of patients with poor prognostic factors. PFS was significantly longer (Cox proportional hazards model) in the VcTD arm than in the TD arm in patients with del(13q), lactate dehydrogenase of > 190 U/L, age > 60 years, t(4;14) with or without deletion of the 17p chromosomal region (del(17p)), high infiltration of bone marrow

plasma cells, and advanced International Staging System (ISS) disease stage (II-III)[8] (see Table 4).

**Table 4. Cox regression analysis of progression free survival in subgroups of patients with poor prognosis**

| | Events*/number of patients | | Hazard ratio (95% CI) | p value† |
|---|---|---|---|---|
| | VTD | TD | | |
| Presence of del(13q) | 29/103 | 46/103 | 0·49 (0·31–0·79) | 0·0039 |
| LDH >190 U/L | 43/182 | 72/200 | 0·60 (0·41–0·87) | 0·0088 |
| Age >60 years | 23/92 | 41/95 | 0·53 (0·32–0·89) | 0·0150 |
| Presence of t(4;14) with or without del(17p) | 20/53 | 32/57 | 0·51 (0·29–0·88) | 0·0174 |
| Bone marrow plasma cells >50% | 30/116 | 41/111 | 0·59 (0·37–0·95) | 0·0301 |
| ISS disease stage II–III | 42/129 | 57/131 | 0·68 (0·46–0·99) | 0·0482 |

VTD=bortezomib with thalidomide plus dexamethasone. TD=thalidomide plus dexamethasone. LDH=lactate dehydrogenase. ISS=international staging system. *Progression, relapse, or death. †Wald $\chi^2$ test.

The sponsor claimed incorporation of VcTD (as opposed to TD) induction and consolidation therapy, into double autologous stem cell transplantation overcame the adverse effect of t(4;14) on PFS. However, the data presented was contradictory. The sponsor stated that in the VcTD arm at 3 years, 69% of patients with the abnormality progressed, relapsed or died compared with 74% of those without the abnormality (p=0.66). In the TD arm at 3 years, 37% of patients with the abnormality progressed, relapsed or died compared with 63% without the abnormality (p=0.0131).

The incidence of patients with del(17p) was small in both arms of the study (VcTD:7%; TD: 8%). This prevents any meaningful analysis of this abnormality on PFS. A multivariate analysis of the overall study population showed that low $\beta_2$-microglobulin concentration, absence of t(4;14) with or without del(17), randomisation to receive VcTD and achievement of CR or nCR were the most important and independent variables with a positive correlation to PFS (see Table 5).

**Table 5. Multivariate analysis of variables favourably affecting progression free survival**

| | Hazard ratio (95% CI) | p value* |
|---|---|---|
| $\beta_2$-microglobulin ≤3·5 mg/L | 0·47 (0·33–0·67) | <0·0001 |
| Absence of t(4;14) with or without del(17p) | 0·51 (0·36–0·73) | 0·0020 |
| Randomisation to receive VTD | 0·64 (0·45–0·90) | 0·0116 |
| Achievement of complete or near complete response | 0·98 (0·97–0·99) | 0·0187 |

VTD=bortezomib with thalidomide plus dexamethasone. *Wald $\chi^2$ test.

[8] Stage I: $\beta_2$-microglobulin (β2M) < 3.5 mg/L, albumin >= 3.5 g/dL; Stage II: β2M < 3.5 mg/L and albumin < 3.5 g/dL; or β2M 3.5 mg/L - 5.5 mg/L irrespective of the serum albumin; Stage III: β2M >= 5.5 mg/L

There was no difference in stem cell mobilisation between treatment groups. Median yields of CD34+ cells were $9.75x10^6$/kg in the VcTD arm and $10.76x10^6$/kg in the TD arm. Some 95% of patients in both arms (VcTD: 209 of 219; TD: 196 of 207) who completed mobilisation achieved sufficient yields for double transplantation. Three patients in the VcTD arm and one patient in the TD arm failed to reach the threshold of at least $2x10^6$ CD 34+ cells per kg to support the need for one transplantation procedure.

**Other Efficacy Studies**

***STUDY IFM 2005-01: Bortezomib plus Dexamethasone is superior to Vincristine plus Doxorubicin plus Dexamethasone as induction treatment prior to autologous stem cell transplantation in newly diagnosed Multiple Myeloma: Results of the IFM 2005-01 Phase III trial.***

*Study design, objectives, location and dates*

This was an open label, Phase III, randomised (1:1:1:1) study which compared the efficacy and safety of VAD (vincristine, adriamycin, dexamethasone) against VcD (bortezomib plus dexamethasone) as induction therapy before high dose melphalan and autologous stem cell transplant (HDT-ASCT) and to evaluate the impact of post induction consolidation therapy (DCEP: dexamethasone, cyclophosphamide, etoposide, prednisone) in patients 18-65 years with newly diagnosed multiple myeloma. The study was conducted at 89 sites in France, Belgium and Switzerland between 9 August 2005 and 18 January 2008. Data cut off for this report was 5 June 2009.

The primary objective of the study was to compare the CR rate (with negative or positive immunofixation) obtained with VAD or VcD up to the end of induction phase.

The secondary objectives were:

- To compare the CR+VGPR+PR rate up to the end of the induction phase obtained with VAD and with VcD.
- To compare the overall CR rate (and CR+VGPR+PR rate) following consolidation treatment with and without DCEP consolidation treatment.
- To preliminarily assess whether achieving CR or VGPR following induction treatment and following DCEP consolidation treatment is associated with prolonged survival.
- To compare toxicity and toxic mortality rate following VAD and following Vel-Dex.
- To compare toxicity and toxic mortality rate following induction treatment alone and following induction treatment plus DCEP consolidation treatment.
- To evaluate the overall CR (and CR+VGPR) rate obtained 1 to 3 months after the first autograft, according to the initial treatment.
- To evaluate the proportion of patients who do not need a second ASCT (according to the induction treatment and each of the 4 treatment arms).

*Inclusion and exclusion criteria*

- Patients with newly diagnosed multiple myeloma, who were at least 18 years and ≤ 65 years of age with Salmon & Durie (SD) Stage II or III disease (see Figure 4), were eligible for inclusion. The other inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (see Figure 5), life expectancy ≥ 2 months and adequate renal (no end stage renal failure requiring dialysis), haematological (platelets ≥ $50x10^9$L and neutrophils ≥ $0.75x10^9$L) and hepatic

(bilirubin ≤ 3 times upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 4 times ULN) function. The key exclusion criteria included confirmed amyloidosis, human immunodeficiency virus (HIV) positive, history of other malignancy (other than basal cell carcinoma and carcinoma in situ of cervix), uncontrolled diabetes, and Grade ≥ 2 peripheral neuropathy (National cancer Institute (NCI)-Common Terminology Criteria (CTC) v 2.0[9]).

All the patients provided informed consent.

**Figure 4. Durie & Salmon Classification**

***Stage I:*** all the following criteria are present:

1. Haemoglobin value > 100g/l
2. Serum calcium value < 120mg/l (3μmol/l)
3. Absence of bone lesion, or solitary bone plasmacytoma.
4. Low monoclonal Ig rate:
    a. IgG < 50g/l
    b. IgA < 30g/l
    c. BJ in the urine < 4g/24h

***Stage II:*** Myeloma with intermediate tumour mass (between 0.6 and $1.2.10^{12}$ cells/m²). Does not correspond to definition of either Stage I .or Stage III.

***Stage III:*** Myeloma with large tumour mass (> $1.2.10^{12}$ cells/m²)

1. Haemoglobin value < 85g/l
2. Serum calcium value > 120mg/l (3μmol/l)
3. Multiple bone lesions
4. High monoclonal Ig rate:
    * IgG > 70g/l
    * IgA > 50g/l
    * BJ in the urine > 12g/24h

[9] Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

**Figure 5. Performance status (ECOG Scale)**

| Grade | Status of the patient |
|---|---|
| 0 | Normal activity without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out light work |
| 2 | Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self care. Totally confined to bed or chair |

*Study treatments*

The patients were randomised (1:1:1:1) to 4 treatment arms: A1 (VAD), A2 (VAD + DCEP), B1(VcD) and B2 (VcD + DCEP). Randomization was stratified by baseline $\beta_2$-microglobulin (> 3 versus ≤ 3 mg/L) and presence of chromosome 13 abnormalities by fluorescence in-situ hybridization analysis (FISH).

The VAD regimen consisted of four 4 week cycles of vincristine 0.4 mg/d, doxorubicin 9 mg/m$^2$/d by continuous infusion on Days 1-4, plus dexamethasone 40 mg orally on Days 1-4 (all cycles), Days 9-12 and Days 17-20 (Cycles 1 and 2).

The VcD regimen consisted of four 3 week cycles of bortezomib 1.3 mg/m$^2$ IV on Days 1, 4, 8, and 11, plus dexamethasone 40 mg on Days 1-4 (all cycles) and Days 9-12 (Cycles 1 and 2).

DCEP regimen consisted of two 4 week cycles of dexamethasone 40 mg orally on Days 1-4, cyclophosphamide 400 mg/m$^2$, etoposide 40 mg/m$^2$ and cisplatin 15 mg/m$^2$/d by continuous infusion on Days 1-4.

The recommended concomitant medications included bisphosphonates (pamindronate 90 mg, zolendronate 4 mg) monthly until first transplantation, plus antibiotics, antiviral and antifungal prophylaxis in accordance with local practice.

Stem cell target yield was 5x10$^6$ CD34+ cells/kg. Stem cell mobilization was undertaken with granulocyte colony stimulating factor (G-CSF) 10µmg/kg/d, from Day 15 of Induction Cycle 3. If the harvest was inadequate, a second mobilization was undertaken with cyclophosphamide 3 g/m$^2$ plus G-CSF 5µmg/kg/d after Induction Cycle 4. Conditioning for the first transplant consisted of melphalan 200 mg/m$^2$. A second transplant was not considered for patients achieving at least VGPR. Patients achieving PR and with a HLA-identical donor could undergo reduced intensity conditioning allogenic stem cell transplant. Patients achieving less than PR or those achieving PR but with no HLA-identical donor could undergo a second autologous transplant. All the patients achieving at least PR post transplantation were to receive 2 months consolidation with lenalidomide followed by lenalidomide maintenance or placebo as per protocol.

Dose modification was required for haematological and non haematological toxicities. The therapeutic agent responsible for all Grade 3 and 4 adverse events was withdrawn until complete recovery and was then reinitiated at a reduced dose. In patients with febrile neutropaenia, (the likely causes are adriamycin and bortezomib) treatment was discontinued until the fever abated. Treatment was also discontinued in patients with Grade 4 haematological toxicity until neutrophils were >$0.75x10^9$/L and platelets were >$50x10^9$/L. Bortezomib related peripheral neuropathy was managed according to established guidelines.

*Efficacy variables and outcomes*

The main efficacy variables were:

- Myeloma protein in blood and urine as tested by electrophoresis and immunofixation.
- Presence/absence of bone marrow plasmocytes.
- Serum calcium levels.
- Presence/absence of soft tissue plasmacytomas.
- Status of bone lesions.

The criteria for response were adapted on the basis of Blades criteria. The required confirmatory second electrophoresis is done 3-4 weeks later, but not if it coincides with the autologous hematopoietic stem cells transplantation (AHSCT).

The study started before international uniform criteria incorporated nCR (defined as CR with positive immunofixation) within VGPR. The study therefore also reports 'at least VGPR' rate as a relevant efficacy parameter.
The primary efficacy outcome was the difference in overall CR rate (with negative or positive immunofixation) obtained with VAD or VcD up to the end of induction phase.

Other efficacy outcomes included:

- To compare the CR+VGPR+PR rate up to the end of the induction phase obtained with VAD and with VcD.
- To compare the overall CR rate (and CR+VGPR+PR rate) following consolidation treatment with and without DCEP consolidation treatment.
- To preliminarily assess whether achieving CR or VGPR following induction treatment and following DCEP consolidation treatment is associated with prolonged survival.
- To evaluate the overall CR (and CR+VGPR) rate obtained 1 to 3 months after the first autograft, according to the initial treatment.
- To evaluate the proportion of patients who do not need a second ASCT (according to the induction treatment and each of the 4 treatment arms).

*Sample size*

With 440 patients and a two-sided $\alpha=0.05$, the study will have a power of 80% to detect a difference of 10% in the rate of CR between induction treatment with four 21 day cycles of VcD and four 28 day cycles of VAD. This is assuming a rate of 20% in the VcD arm versus 10% in the VAD arm. On this basis, the four arms of the study (A1, A2, B1, and B2) will have 110 patients each. Determination of the rate of CR after induction treatment would be based on the combined patient population of A1 and A2 versus B1 and B2.

*Randomisation and blinding methods*

The patients were randomised (1:1:1:1) to 4 treatment arms: A1 (VAD), A2 (VAD + DCEP), B1 (VcD) and B2 (VcD + DCEP). Randomization was stratified by baseline $\beta_2$-microglobulin (> 3 versus ≤ 3 mg/L) and presence of chromosome 13 abnormalities. Randomization was centralised. The study was not blinded.

*Statistical methods*

The study has 80% power (two sided $\alpha$=0.05) to demonstrate a 15% CR/nCR benefit with the addition of DCEP consolidation to the VAD (10% to 25%) or Vel-Dex (20% to 35%) arms. Comparisons of response rates, including the primary efficacy analysis, as well as comparisons of patients using/not using DCEP consolidation therapy, will use the Cochran-Mantel-Haenszel chi square test adjusting for the stratification factors. Comparisons of time-to-event data were performed using the log rank test; distributions were estimated using the Kaplan-Meier method. PFS was defined as time from treatment start to progression, relapse or death. The intent-to-treat (ITT) population is defined as all the patients who have been randomised. Safety was evaluated in all the patients who received at least one dose of study drug. Rates of adverse events were compared using the Cochran-Mantel-Haenszel chi square test adjusting for the stratification factors.

*Participant flow*

A total of 493 patients were enrolled and of these 482 were randomly assigned; 242 received induction with VAD (A1:121, A2:121) and 240 received VcD (B1:121, B2:119). The distribution of patients remained even during the course of the study. The evaluable patients included 218 in the VAD arm and 223 in the VcD arm; 24 and 17 patients, respectively, were discontinued from the study. The reasons for discontinuations included protocol violations, disease progression and adverse events.

*Baseline data*

There were no significant differences between the VAD and VcD arms. The distribution of patients with $\beta_2$-microglobulin and chromosome 13 abnormalities at baseline was even.

*Results for the primary efficacy outcome*

The post induction rate for CR/nCR was significantly better in the VcD arm (B1: 14.8%) than in the VAD arm (A1: 6.4%). The 'at least VGPR' rate was similarly better in the VcD arm than in the VAD arm (37.7% versus 15.1%; p<0.001). The overall response rates, regardless of ISS disease stage or cytogenetic abnormalities, were better in the VcD arm. The 'at least VGPR' and the CR/nCRrates for Stage I, II and III disease remained comparable while the corresponding rates in the VAD arm declined with worsening stage. Patients with cytogenetic abnormalities appear to have a better response to VcD therapy than to VAD therapy (see Table 6).

**Table 6. Bortezomib and Dexamethasone versus AD prior to ASCT in MM**

| Patients | VAD (A1 + A2) (n = 242) No. | % | Bortezomib Plus Dexamethasone (B1 + B2) (n = 240) No. | % | P |
|---|---|---|---|---|---|
| Evaluable population | 218 | | 223 | | |
| ORR (at least PR) | 137 | 62.8 | 175 | 78.5 | < .001 |
| At least VGPR | 33 | 15.1 | 84 | 37.7 | < .001 |
| CR/nCR | 14 | 6.4 | 33 | 14.8 | .004 |
| CR | 3 | 1.4 | 13 | 5.8 | .012 |
| MR + SD | 58 | 26.6 | 28 | 12.6 | |
| PD | 9 | 4.1 | 10 | 4.5 | |
| Death | 6 | 2.8 | 1 | 0.5 | |
| Not assessable | 8 | 3.7 | 9 | 4.0 | |
| ORR and at least VGPR and CR/nCR response rates by disease stage | | | | | |
| ISS 1 | 97 | | 102 | | |
| ORR | 65 | 67.0 | 83 | 81.4 | .017 |
| At least VGPR | 20 | 20.6 | 38 | 37.3 | .001 |
| CR/nCR | 11 | 11.3 | 16 | 15.7 | .325 |
| ISS 2 | 82 | | 81 | | |
| ORR | 47 | 57.3 | 58 | 71.6 | .059 |
| At least VGPR | 11 | 13.4 | 29 | 35.8 | .001 |
| CR/nCR | 4 | 4.9 | 12 | 14.8 | .044 |
| ISS 3 | 54 | | 52 | | |
| ORR | 31 | 57.4 | 40 | 76.9 | .034 |
| At least VGPR | 4 | 7.4 | 21 | 40.4 | < .001 |
| CR/nCR | 0 | | 7 | 13.5 | .006 |
| ORR, and at least VGPR and CR/nCR response rates by cytogenetics | | | | | |
| del(13) by FISH | 103 | | 101 | | |
| ORR | 67 | 65.1 | 79 | 78.2 | .037 |
| At least VGPR | 15 | 14.6 | 47 | 46.5 | < .001 |
| CR/nCR | 6 | 5.8 | 21 | 20.8 | .002 |
| No del(13) | 139 | | 139 | | |
| ORR | 80 | 57.6 | 106 | 76.3 | .001 |
| At least VGPR | 21 | 15.1 | 42 | 30.2 | .003 |
| CR/nCR | 9 | 6.5 | 14 | 10.1 | .276 |
| $\beta_2$-microglobulin > 3 mg/L and del(13) | 65 | | 63 | | |
| ORR | 42 | 64.6 | 45 | 71.4 | .409 |
| At least VGPR | 10 | 15.4 | 27 | 42.9 | .001 |
| CR/nCR | 3 | 4.6 | 12 | 19.1 | .011 |
| t(4;14) and/or del(17p) | 29 | | 40 | | |
| ORR | 17 | 58.6 | 28 | 70.0 | .327 |
| At least VGPR | 5 | 17.2 | 16 | 40.0 | .043 |
| CR/nCR | 1 | 3.5 | 7 | 17.5 | .072 |
| Neither t(4;14) nor del(17p) | 213 | | 200 | | |
| ORR | 130 | 61.0 | 157 | 78.5 | < .001 |
| At least VGPR | 31 | 14.6 | 73 | 36.5 | < .001 |
| CR/nCR | 14 | 6.8 | 28 | 14.0 | .013 |

NOTE. All response assessments were confirmed by an independent review committee.
Abbreviations: VAD, vincristine plus doxorubicin plus dexamethasone; A1, VAD plus no consolidation; A2, VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation; B1, bortezomib plus dexamethasone (BD) with no consolidation; B2, BD plus DCEP consolidation; ORR, overall response rate; PR, partial response; VGPR, very good partial response; CR/nCR, complete response/near CR; MR, minimal response; SD, stable disease; PD, progressive disease; ISS, International Staging System; FISH, fluorescent in situ hybridization.

*Results for other efficacy outcomes*

Among patients who received DCEP consolidation therapy, the CR/nCR rate in the VcD arm (B2; n=96) was 26% (B1: 15.4%) and in the VAD arm (A2; n=91) 8% (A1: 8.2%). The corresponding 'at least VGPR' rates in the VcD arm (B2) was 50% (B1: 41.1%) and in the VAD arm (A2) 22% (A1: 15.4%). Therefore the 'at least VGPR' rate in the VcD induction only arm (B1) was better than the 'at least VGPR' rate in the VAD induction plus DCEP consolidation arm (A2).

Stem cell yields of > $2x10^6$ $CD34^+$ cell/kg were achieved by 96% in the VcD arm and 98% in the VAD arm. Stem cell transplantation was carried out in 197 (88.3%) in the VcD arm and184 (84.4%) patients in the VAD arm. The post first transplantation CR rates in the evaluable population in the VcD and VAD arms were 16.1% and 8.7%, respectively. The corresponding CR/nCR rates were 35% and 18.4%, respectively, and the at least VGPR rates were 54.3% and 37.2%, respectively. Overall, including post second transplantation,

the response rates were significantly higher in the VcD arm (see Table 7). A second transplant was indicated for those patients who did not achieve 'at least VGPR' following the first transplant. This was so for 76 patients (38.6%) in the VcD arm and 103 patients (56%) in the VAD arm. However, of these, only 41 patients in the VcD arm and 50 patients in the VAD arm received a second transplantation.

**Table 7. Response to first transplantation and overall at least VGPR and CR/nCR rates, including second transplantation, among all evaluable patients**

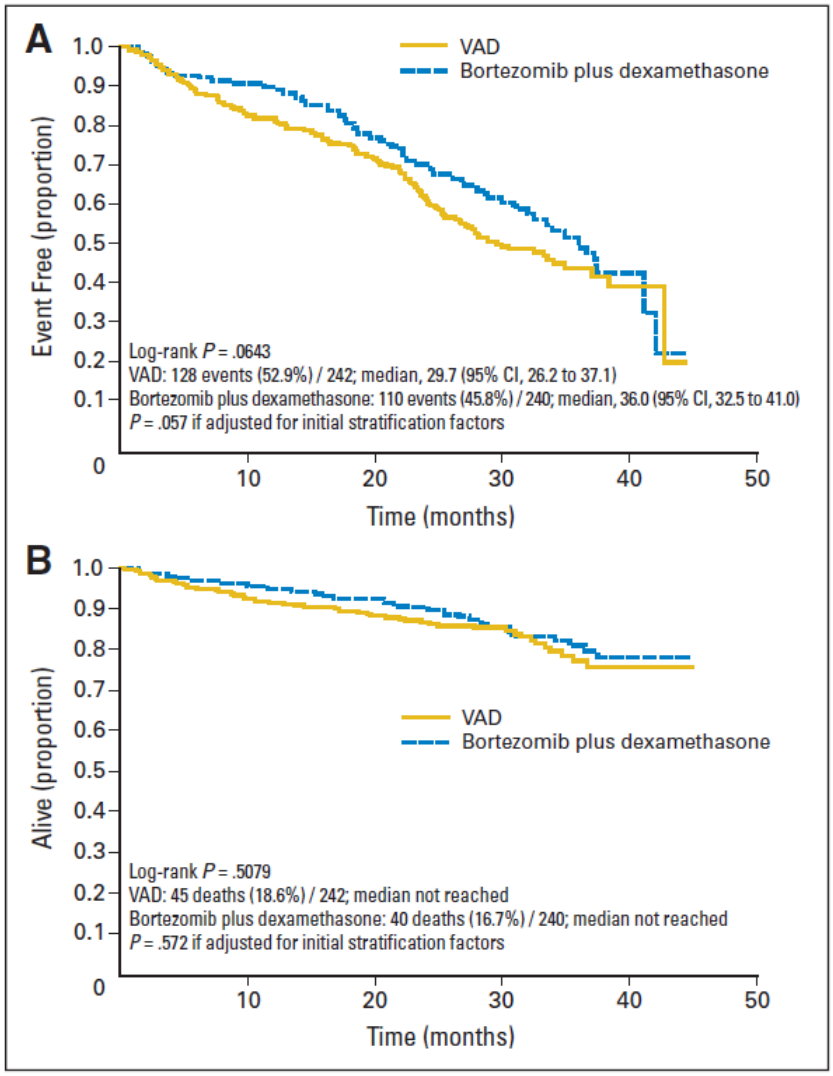
| | VAD (A1 + A2) (n = 218) | | Bortezomib Plus Dexamethasone (B1 + B2) (n = 223) | | |
|---|---|---|---|---|---|
| Response | No. | % | No. | % | *P* |
| Response to first transplantation | | | | | |
| ORR (at least PR) | 168 | 77.1 | 179 | 80.3 | .401 |
| At least VGPR | 81 | 37.2 | 121 | 54.3 | < .001 |
| CR/nCR | 40 | 18.4 | 78 | 35.0 | < .001 |
| CR | 19 | 8.7 | 36 | 16.1 | .016 |
| MR + SD + PD | 8 | 3.7 | 6 | 2.7 | |
| Death | 2 | 0.9 | 1 | 0.5 | |
| No transplantation | 34 | 15.6 | 26 | 11.7 | |
| Overall, including second transplantation | | | | | |
| At least VGPR | 102 | 46.7 | 151 | 67.7 | < .001 |
| CR/nCR | 49 | 22.5 | 88 | 39.5 | < .001 |

NOTE. All response assessments were confirmed by an independent review committee.

Abbreviations: VGPR, very good partial response; CR/nCR, complete response/near CR; VAD, vincristine plus doxorubicin plus dexamethasone; A1, VAD plus no consolidation; A2, VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation; B1, bortezomib plus dexamethasone (BD) with no consolidation; B2, BD plus DCEP consolidation; ORR, overall response rate; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

The median PFS was 36 months in the VcD arm and 29.7 months in the VAD arm. In all, after median follow up of 31.2 months, 45.8% (110 of 242 patients) in the VcD arm and 52.9% (128 of 242 patients) in the VAD arm had progressed (p=0.064). The median OS had not been reached in either group after median follow up of 32.2 months with 40 patients (16.7%) in the VcD arm and 45 patients (18.6%) in the VAD arm having died (p=0.508). The respective 3 year OS rates for the VcD and VAD arms were 81.4% and 77.4%, respectively (see Figure 6 below).

**Figure 6. (A) Progression free survival and (B) overall survival according to induction therapy received for all randomised patients. VAD, vincristine plus doxorubicin plus dexamethasone**




After transplantation, 153 patients each from the VAD and VcD arms received further treatment; 127 (83%) and 140 (91.5%), respectively, were enrolled onto protocol IFM 2005-02 and received lenalidomide consolidation before random assignment to lenalidomide maintenance or placebo. Additionally, 4 patients from each group received lenalidomide maintenance and 15 VAD patients and 8 VcD patients received thalidomide maintenance.

### Studies in abstract form

Two studies (HOVON and PETHEMA) were submitted in abstract form and the respective protocols were available.

***Study HOVON: A randomised Phase III trial comparing bortezomib, adriamycin and dexamethasone (PAD) versus vincristine, adriamycin and dexamethasone (VAD) as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM).***

This randomised open label Phase III trial comparing bortezomib, adriamycin and dexamethasone (PAD) versus vincristine, adriamycin and dexamethasone (VAD) as

induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM), was conducted in 75 referral centres in the Netherlands, Belgium and Germany between May 4 2005 and May 16 2008. Some 825 patients were recruited. This is the report of the planned interim analysis of response after induction and HDM-1 of the initial 300 (150 per arm) randomised patients.

The study objectives included the assessment of efficacy, as measured by progression free survival (PFS), overall response rate, overall survival and assessment of safety and toxicity.

The primary endpoint was PFS. The secondary endpoints were response rates (PR, VGPR, and CR), overall survival measured from time of registration, PFS from last high dose melphalan (HDM) treatment to progression or death from any cause for patients who received at least PR on HDM, and toxicity.

Patients with Salmon & Durie (SD) Stage II or III disease, aged 18-65 years, with a WHO performance status 0-3[10] were included. Patients who had previous chemotherapy or radiotherapy, except 2 cycles of melphalan/prednisone or local radiotherapy in case of local melanoma, were excluded.

The patients were randomly assigned to treatment arms A or B. Treatment consisted of 3 cycles of induction therapy. Arm A receive vincristine (0.4 mg/d), adriamycin (9 mg/m$^2$/d by continuous infusion on Days 1-4), and dexamethasone (40 mg orally on Days 1-4 in all cycles, Days 9-12 and Days 17-20 in Cycles 1 and 2). Arm B receive bortezomib (1.3 mg/m$^2$ intravenously on Days 1, 4, 8, and 11), adriamycin (9 mg/m$^2$/d by continuous infusion on Days 1-4) and dexamethasone (40 mg on Days 1-4 in all cycles), and Days 9-12 in Cycles 1 and 2). Stem cell mobilization and collection was achieved using the CAD regimen (cyclophosphamide, Adriamycin and dexamethasone chemotherapy followed by G-CSF). This was followed by treatment with high dose melphalan and stem cell transplantation. Maintenance treatment with thalidomide or bortezomib was commenced 4 weeks later and continued for 2 years.

The study scheme is described in Figure 7. The two randomised arms (150 in each arm) were well matched for SD stage of disease, ISS stage and distribution of chromosomal abnormalities. The completion rates were equally distributed between treatment arms. Stem cell apheresis was successful in all the patients who received CAD.

[10] WHO performance scale: The World Health Organization (WHO) designed the scale which has categories from 0 to 4 as follows:

0 : fully active and more or less as you were before your illness

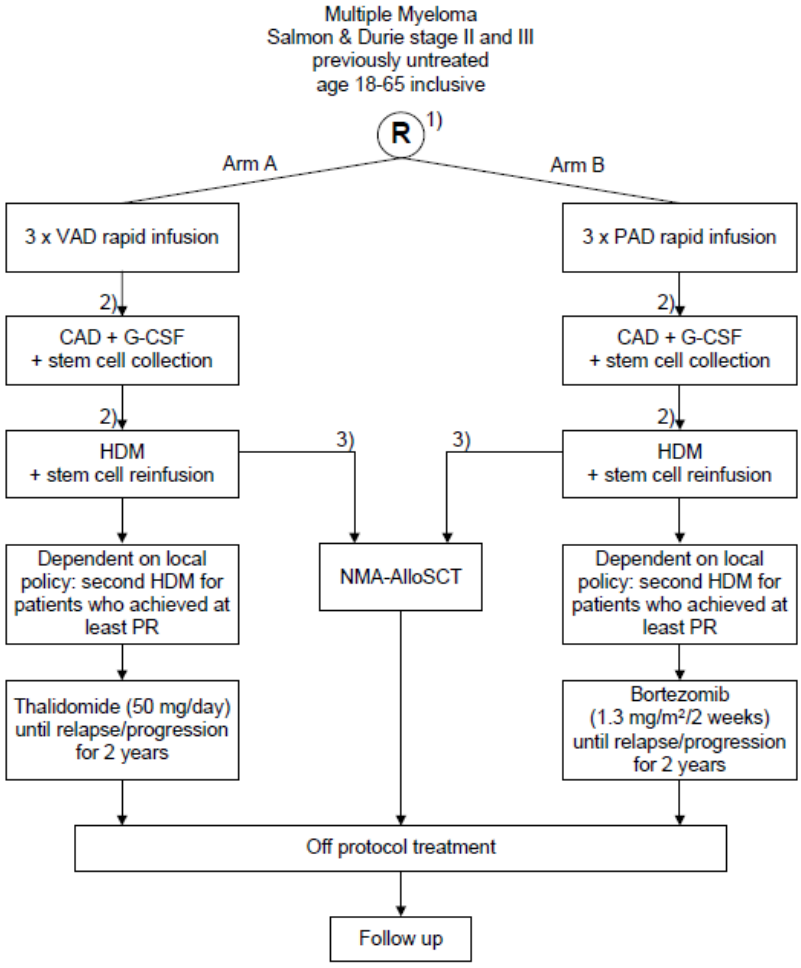
1 - cannot carry out heavy physical work, but can do anything else

2 - up and about more than half the day; you can look after yourself, but are not well enough to work

3 - in bed or sitting in a chair for more than half the day; you need some help in looking after yourself

4 - in bed or a chair all the time and need a lot of looking after

**Figure 7. Scheme of study.**




1) Inclusion of patients in the ongoing Zoledronate trials is strongly recommended.

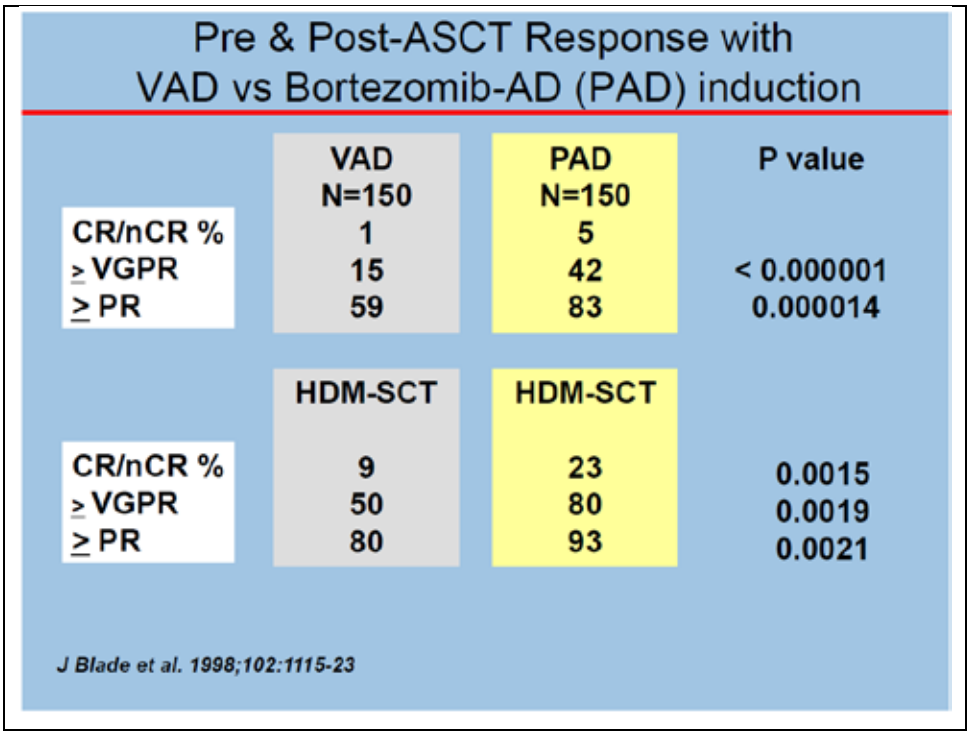
2) Patients who do not meet the inclusion criteria for CAD or HDM but with a CR, PR or MR, may proceed with 3 more cycles of VAD (Arm A) or PAD (Arm B), followed by Thalidomide maintenance (Arm A) or Bortezomib maintenance (Arm B) for 2 years until progression.

3) Patients with an HLA-identical family donor who meet the egilibility criteria proceed with non-myeloablative allogeneic stem cell transplantation after the first course of HDM. It is strongly recommended to include patients in ongoing non-myeloablative AlloSCT trials.

The overall response rate (PR or better), as assessed by EBMT criteria, was significantly better in the PAD arm (83%) than that in the VAD arm (59%). The response rates were better after HDM-1 as well. The results were statistically significant (see Table 8). The sponsor states that deletion of chromosome 13q did not have a significant impact on response.

PFS was not addressed in this interim analysis.

**Table 8. Pre and Post-ASCT response with VAD versus Bortezmib-AD (PAD) induction.**




***Study PETHEMA: A Phase III national, open label, multicenter, randomised, comparative study of VBMCP-VBAD*/Velcade versus thalidomide/dexamethasone versus Velcade/thalidomide/dexamethasone in patients with newly diagnosed, symptomatic multiple myeloma aged 65 years or less.***

The Spanish Myeloma Group activated this randomised Phase III trial to compare VBMCP/VBAD versus TD versus VcTD in April 2006. Patients were randomised 1:1:1 into groups A (VBMCP-VBAD/Velcade), B (thalidomide/dexamethasone) and C (VcTD). Group A received 4 alternating VBMCP/VBAD cycles of chemotherapy . This was followed by 2 cycles of velcade with a 10 day rest in between. Group B received six, 4 week cycles of thalidomide and dexamethasone. Patients in group C received six, 4 week cycles of velcade, thalidomide and dexamethasone. Stem cell mobilization (with G-CSF) and collection was performed at least 4 weeks after last induction chemotherapy cycle, provided there was no disease progression or unacceptable toxicity. Autologous transplantation was performed with melphalan as conditioning treatment. Three months after transplantation, all the patients, irrespective of their assigned induction treatment group, were randomised 1:1:1. Group M1 received interferon α-b, three times per week, for 3 years. Group M2 received thalidomide daily for 3 years. Group M3 received thalidomide daily for 3 years and velcade on Days 1, 4, 8 and 11, every 3 months for 3 years. All the patients were given bisphosphonates every 3 to 4 weeks for at least the first two years.

The protocol for dose delay and dose changes was similar to that in the other studies.

The study design during induction treatment and maintenance treatment were described in the study report. Patients with symptomatic multiple myeloma (MM), aged ≤ 65 years, with measurable disease and a life expectancy > 3 months were included in the study. Exclusion factors included previous treatment for MM, ≥ Grade 2 peripheral neuropathy in the past 14 days and presence of HIV, hepatitis B or hepatitis C infection. Patients were

withdrawn from the study if there was disease progression or the development of unacceptable adverse events.

A total of 390 patients were planned to be randomised equally in the three groups.

The primary efficacy endpoints were the response rate to the three induction regimens, the CR rate following autologous transplantation and the response during maintenance treatment. The secondary efficacy endpoints included survival (OS, PFS, response duration and TTP), safety and tolerability of the three induction regimens, the PBSC mobilization capacity of the 3 induction regimens and changes in PRO scores.

275 of the planned 390 patients were enrolled. As of 15 February 2008, 190 patients (96 males, 94 females), of median age 57 years had entered the study. Of these, 32 patients (17%) had extramedullary plasmacytomas (EMP). The stages, based on the ISS classification, were: Stage I (38%), Stage II (41%), Stage III (20%) and unknown (1%).

Some 173 patients (group A=58, group B=61 and group C=54) were already evaluable for response and toxicity to induction therapy. Efficacy and toxicity were assessed on an intent-to-treat (ITT) basis. The ≥ PR rate was 70%, 62% and 77% in groups A (VBMCP-VBAD/velcade), B (TD), and C (VcTD), respectively. The result was non-significant. The immunofixation negative CR rate was significantly higher in groups A (22%) and C (31%) than in group B (6%) $p<0.01$. Progressive disease was significantly higher in patients with extramedullary plasmacytoma (EMP) (31% versus 12%; $p=0.01$). The higher progressive disease rate in patients with EMP was similar in the three arms of the study.

**Phase I/II Studies**

Various Phase I/II studies were provided. Study details, including study protocols were not available.

***Prospective randomised studies***

**Ludwig *et al*:** This Phase II randomised controlled trial (RCT) which compared VcTD with VcTD plus cyclophosphamide (VcTDC) in 49 patients with MM. The follow up period was 9.7 months. The rates for CR were 45% and 35% in the VcTD and VcTDC arms, respectively, post-induction. The corresponding rates post transplant (with ASCT) were 58% and 48%, respectively. The VGPR rates were superior in the VcTD arm post induction and post transplant.

***Prospective non randomised studies***

There were nine Phase II studies in this category which examined the effects of bortezomib alone or in combination with a number of other treatment agents including dexamethasone (VcD: Jagannath *et al*), doxorubicin plus dexamethasone (VcAD: Palumbo *et al*), cyclophosphamide plus dexamethasone (VcCD: Bessinger *et al*), thalidomide and dexamethasone (VcTD: Bessinger *et al*), melphalan and prednisone (VcMP: Gasparetto *et al*) and DT-PACE (VcDT-PACE: Jakubowiak *et al*, Barlogie *et al*). In some of the studies, the patient population contained both transplant eligible and transplant ineligible patients. The post-induction overall response rates ranged from 83% to 100%. The median PFS was reported in two studies and was 21 months in one (Jagannath *et al*) and 24 months in the other (Barlogie *et al*).

***Retrospective studies***

In both retrospective studies the treatment regimen that was analysed was VcTD.

Wang *et al* reported an overall response rate of 87% following induction and 95% following transplantation in 38 patients with newly diagnosed MM who had 15 months follow up.

Kaufman *et al* reported an overall response rate of 91% following induction and 100% following transplantation in 34 patients with newly diagnosed MM who had 25 months follow up. The median PFS was 27.4 months.

### *Other Studies of bortezomib associated treatment regimens*

The other studies that were listed had bortezomib in combination with thalidomide and dexamethasone, (VcTD), thalidomide (VcT), and lenalidomide and dexamethasone (LVcD). These studies examined a variety of patient populations.

#### Evaluator's Conclusions on Clinical Efficacy

The four studies that were examined (two published Phase III studies and two abstracts of Phase III studies) were RCTs with active comparators. Randomisation was computer generated and the treatment arms in all the studies were balanced. The GIMEMA study (pivotal study) compared the efficacy of induction with thalidomide plus dexamethasone alone and in combination with bortezomib. Consolidation treatment was with VcTD or TD followed by maintenance treatment with dexamethasone. The IFN-2005 study examined the efficacy of induction with bortezomib in combination with dexamethasone against a combination of vincristine, Adriamycin and dexamethasone. Consolidation treatment with DCEP was given to approximately half the population in each treatment group. The HOVON-65 study compared the efficacy of induction treatment with bortezomib in combination with Adriamycin and dexamethasone against vincristine in combination with Adriamycin and dexamethasone. The PETHEMA study examined the efficacy of induction treatment of three chemotherapy regimens. Two of the regimens contained bortezomib. In all the studies, induction treatment (3 to 6 cycles) was followed by high dose melphalan with stem cell transplant.

Based on recommendation from the American Society of Haematology and the FDA, all the studies used response rates as surrogate for overall survival and progression free survival; which are the usual endpoints. The definitions of response rates that were used were common to all the studies.

The study populations were similar because selection criteria across the studies were similar. The same dose of bortezomib was used in all the studies, although the cycle lengths differed.

The CR/nCR rates in patients treated with bortezomib based treatments as induction treatment (VcTD; VcD; VcAD; VBMCP/VBAD/bortezomib) were significantly better than the rates achieved in the respective comparator treatment groups. The superior rates in the bortezomib based groups were seen post transplant as well. The use of consolidation treatment with VcTD or DCEP was associated with further improvement in response rates. The estimated 3 year rate of progression free survival was significantly higher in the bortezomib treatment based group in the GIMEMA study.

The results suggest that bortezomib, as induction therapy and when used as consolidation, has a beneficial effect on response rates. The various Phase I/II studies that were submitted by the sponsor were supportive of induction therapy with bortezomib associated treatment regimens.

## Safety

#### Studies Providing Evaluable Safety Data

The following studies provided evaluable safety data:

**Pivotal studies:**

- GIMEMA: VcTD compared with TD as induction therapy before and consolidation therapy after double autologous stem cell transplantation in newly diagnosed multiple myeloma. This was a randomised Phase 3 study.

**Non-pivotal studies:**

- IFM 2005-01: VcD is superior to VAD as induction treatment prior to autologous stem cell transplantation in newly diagnosed MM.
- HOVON: A randomised Phase III study in patients with MM comparing the effect of VAD (vincristine, adriamycin, dexamethasone) versus PAD (bortezomib, adriamycin, dexamethasone) for induction treatment, followed by intensive chemotherapy with high dose melphalan followed by maintenance therapy with thalidomide or bortezomib.
- PETHEMA: A Phase III national, open label, multicenter, randomised, comparative study of VBMCP-VBAD*/Velcade versus thalidomide/dexamethasone versus Velcade/thalidomide/dexamethasone in patients with newly diagnosed, symptomatic multiple myeloma aged 65 years or less.

The limited safety data provided in this literature based submission could not be effectively evaluated using the TGA evaluation template. The safety evaluation will be presented with reference, wherever possible, to the format of the safety template.

In the studies, the following safety data were collected:

General adverse events: All adverse events that occur between the first study related procedure and 30 days after the last dose of study drug were graded by NCI-CTC v2.0. Adverse Events were recorded in the source document and reported at the end of each cycle of treatment. They were externally monitored and centrally reassessed. All serious adverse events were reported within 24 hours of the event.

AEs of particular interest, including peripheral neuropathy and thrombosis, were carefully assessed. The protocols did not specify the methods used.

Laboratory tests, including serum and urine protein evaluations, haematology tests (haemoglobin (Hb), white blood cells (WBC), and platelet count), clinical chemistry (liver function test (LFT), urea and electrolytes) and bone marrow aspirate were performed at prescribed intervals, as described in the study schedules.

In the GIMEMA study, the safety population consisted of 236 patients in the VcTD arm and 238 patients in the TD arm. The patients received three 21 day cycles of induction therapy and two 35 day cycles of consolidation therapy with VcTD or TD. Patients in the VcTD arm received 94% of planned bortezomib, 88% of planned thalidomide and 94% of planned dexamethasone. In the TD arm, the patients received 91% of planned thalidomide and 93% of planned dexamethasone. Rates of adverse events were compared between treatment groups with the chi square ($\chi^2$) test. There were significantly more Grade 3/4 adverse events in the VcTD arm than in the TD arm (56% versus 33%; $p<0.0001$). Non haematological adverse events were more common in the VcTD arm than in the TD arm (see Table 9). The most common Grade 3 & 4 adverse events (> 10%) were skin rash and peripheral neuropathy. Cardiac toxicity was reported by 2% in each treatment arm.

Of the 23 patients (10%) in the VcTD arm who had Grade 3 (n=22) or Grade 4 (n=1) neurological toxic effects during induction therapy, two patients with treatment emergent peripheral neuropathy were discontinued from the study (see Table 10). Resolution of

Grade 3 or 4 peripheral neuropathy or improvement by at least one grade was reported in 18 of the 23 patients in the VcTD arm within a median of 26 days from onset and in 3 of 5 patients in the TD arm within 39, 48 and 67 days from onset. The types of Grades 3 or 4 adverse events reported during consolidation therapy were similar to those reported during induction therapy. Two patients receiving VcTD consolidation therapy developed Grade 3/4 peripheral neuropathy. No such cases occurred in the TD arm.

**Table 9. Non haematological adverse events of any grade reported in at least 10% of patients during induction therapy.**

| | VTD (n=236) | | TD (n=238) | |
|---|---|---|---|---|
| | Grade 1–4 | Grade 3–4 | Grade 1–4 | Grade 3–4 |
| Constipation | 99 (42%) | 10 (4%) | 67 (28%) | 7 (3%) |
| Neuropathy | 80 (34%) | 23 (10%) | 34 (14%) | 5 (2%) |
| Skin rash | 67 (28%) | 24 (10%) | 17 (7%) | 4 (2%) |
| Fever | 28 (12%) | 3 (1%) | 24 (10%) | 3 (1%) |
| Infections | 24 (10%) | 7 (3%) | 35 (15%) | 11 (5%) |
| Oedema | 25 (11%) | 2 (1%) | 13 (5%) | 2 (1%) |
| Gastrointestinal events (excluding constipation) | 46 (19%) | 5 (2%) | 19 (8%) | 1 (<1%) |

Data are number (%). VTD=bortezomib with thalidomide plus dexamethasone. TD=thalidomide plus dexamethasone.

**Table 10. Serious adverse events and Grade 3 or 4 adverse events reported in at least 2% of patients during induction therapy**

| | VTD (n=236) | TD (n=238) | p value |
|---|---|---|---|
| Any serious adverse event | 31 (13%) | 30 (13%) | 0·86 |
| Any grade 3 or 4 adverse event | 132 (56%) | 79 (33%) | <0·0001 |
| Any grade 3 or 4 non-haematological adverse event | 120 (51%) | 73 (31%) | <0·0001 |
| Skin rash | 24 (10%) | 4 (2%) | 0·0001 |
| Peripheral neuropathy | 23 (10%) | 5 (2%) | 0·0004 |
| Deep vein thrombosis | 8 (3%) | 12 (5%) | 0·53 |
| Constipation | 10 (4%) | 7 (3%) | 0·45 |
| Infections excluding herpes zoster | 7 (3%) | 11 (5%) | 0·35 |
| Gastrointestinal events (excluding constipation) | 5 (2%) | 1 (<1%) | 0·0982 |
| Cardiac toxicity | 5 (2%) | 5 (2%) | 0·99 |
| Liver toxicity | 4 (2%) | 7 (3%) | 0·37 |
| Discontinuation during or after induction therapy | 13 (6%) | 26 (11%) | 0·0319 |
| Toxic effects | 10 (4%) | 7 (3%) | 0·45 |
| Disease progression | 0 | 12 (5%) | <0·0001 |
| Other reasons | 2 (1%) | 7 (3%) | 0·21 |
| Early death | 1 (<1%) | 0 | 0·31 |

Data are number (%). VTD=bortezomib with thalidomide plus dexamethasone. TD=thalidomide plus dexamethasone.

In the IFM 2005-01 trial, the safety population consisted of 239 patients in each treatment arm (VAD arm: 910 cycles; and VcD arm: 930 cycles). The rates of adverse events were compared between the two treatment groups using the Cochran-Mantel-Haenszel $\chi^2$ test adjusted for stratification factors. Anaemia, neutropaenia and thrombosis were significantly more frequent in the VAD arm. The incidence of peripheral neuropathy was very high in the VcD arm (45.6% versus 28% in VAD arm). The high incidence of peripheral neuropathy was because the Medical Dictionary for Regulatory Activities (MedDRA)[11] preferred terms used by investigators considered related to neurological toxicity by the Principal Investigator, were included in the totals for peripheral neuropathy. However, Grade 3/4 peripheral neuropathy was 7.1% in the VcD arm and 2.1% in the VAD arm. Deaths were reported in 12 patients (7 infections, 3 haemorrhages and 2 disease progression) in the VAD arm and 2 patients (1 infection and 1 disease progression) in the VcD arm during the study. Herpes zoster infection more common in the VcD arm (see Table 11).

[11] MedDRA is a clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process. The MedDRA dictionary is organized by System Organ Class (SOC), divided into High-Level Group Terms (HLGT), High-Level Terms (HLT), Preferred Terms (PT) and finally into Lower-Level Terms (LLT).

**Table 11. Safety profiles of induction therapy with VAD and bortezomib plus dexamethasone, including most common and other important haematologic and non-haematologic toxicities**

| Variable | VAD (A1 + A2) (n = 239) | | | | Bortezomib Plus Dexamethasone (B1 + B2) (n = 239) | | | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| Any AE | 219 | 91.6* | | | 231 | 96.7* | | |
| Any grade ≥ 3 AE | 110 | 46.0 | | | 112 | 46.9 | | |
| Any grade ≥ 4 AE | 37 | 15.5 | | | 27 | 11.3 | | |
| Any serious AE | 81 | 33.9 | | | 65 | 27.2 | | |
| Toxicity leading to study drug discontinuation or delay | 32 | 13.4 | | | 44 | 18.4 | | |
| Toxicity leading to bortezomib dose reduction, No. of cycles | | | | | 64 of 931 | 6.9 | | |
| Death related to toxicity | 7 | 2.9* | | | 0* | | | |
| | Grade 1-4 | | Grade 3-4 | | Grade 1-4 | | Grade 3-4 | |
| Hematologic toxicities | | | | | | | | |
| Anemia | 51 | 21.3 | 21 | 8.8* | 38 | 15.9 | 10 | 4.2* |
| Neutropenia | 33 | 13.8* | 24 | 10.0* | 19 | 8.0* | 12 | 5.0* |
| Thrombocytopenia | 11 | 4.6* | 3 | 1.3 | 26 | 10.9* | 7 | 2.9 |
| Infections | 91 | 38.1* | 29 | 12.1 | 115 | 48.1* | 21 | 8.8 |
| Herpes zoster† | 5 | 2.1* | — | | 22 | 9.2* | — | |
| Thrombosis | 29 | 12.1* | 13 | 5.4* | 11 | 4.6* | 4 | 1.7* |
| Nonhematologic toxicities | | | | | | | | |
| Fatigue | 50 | 20.9 | | | 68 | 28.5 | | |
| Rash | 21 | 8.8 | | | 28 | 11.7 | | |
| GI symptoms | 75 | 31.4 | | | 64 | 26.8 | | |
| Cardiac disorders | 14 | 5.9 | | | 14 | 5.9 | | |
| Pneumopathy | 15 | 6.3 | | | 8 | 3.4 | | |
| Peripheral neuropathy‡ | 67 | 28.0* | | | 109 | 45.6* | | |
| Peripheral neuropathy grade | | | | | | | | |
| 1 | 42 | 17.6 | | | 51 | 21.3 | | |
| 2 | 19 | 8.0* | | | 37 | 15.5* | | |
| 3-4 | 5 | 2.1* | | | 17 | 7.1* | | |

Abbreviations: VAD, vincristine plus doxorubicin plus dexamethasone; A1, VAD plus no consolidation; A2, VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation; B1, bortezomib plus dexamethasone (BD) with no consolidation; B2, BD plus DCEP consolidation; AE, adverse event.

*$P < .05$ for comparison of AE rate between VAD and bortezomib plus dexamethasone.

†No antiviral prophylaxis for herpes zoster was specified in the protocol.

‡The following Medical Dictionary for Regulatory Activities (MedDRA) –preferred terms used by investigators were considered related to neurologic toxicity by the principal investigator and included in the totals for peripheral neuropathy: accommodation disorder, anosmia, areflexia, difficulty in walking, dysesthesia (no essential change), fall, formication, hypoesthesia, hyporeflexia, muscle spasms, neuralgia (not otherwise specified [NOS]), neuralgic amyotrophy, neurologic disorder NOS, pain in limb, paraparesis, paresthesia, peripheral neuropathy aggravated, peripheral motor neuropathy, peripheral neuropathy NOS, peripheral sensory neuropathy, polyneuropathy NOS, sensory loss, vertigo, vision blurred.

In the HOVON-65 trial, 300 patients completed the PAD/VAD with no difference between treatment arms. Full dose bortezomib was administered to 95%, 79%, and 85% of

patients in Cycles 1, 2 and 3, respectively. The incidence of any adverse event was 82% in the VAD arm and 87% in the PAD arm. The incidence of Grade ≥ 3 adverse event was 53% in the VAD arm and 59% in the PAD arm (see Table 12). The incidence of CTC grade 3/4 polyneuropathy was significantly greater in the PAD arm than in the VAD arm (16% versus 6%; p=0.003) (see Table 13). Constitutional symptoms were also more common in the PAD arm (30% versus 24%). DVT and pulmonary embolism was more frequently reported in the VAD arm (10%) than in the PAD arm (6%).

**Table 12. Toxicities during induction**

| | VAD N = 149 | PAD N = 149 |
|---|---|---|
| Any AE, n (%) | 122 (82%) | 129 (87%) |
| Grade ≥ 3, n (%) | 79 (53%) | 88 (59%) |
| Grade ≥ 4, n (%) | 18 (12%) | 32 (21%) |
| SAE, n (%) | 52 (35%) | 67 (45%) |
| AE leading to study drug discontinuation, n (%) | 5 (3%) | 9 (6%) |
| AE leading to death, n (%) | 6 (4%) | 3 (2%) |

**Table 13. Non haematologic toxicity Grade 2-4**

| | VAD N = 149 | PAD N = 149 | P value |
|---|---|---|---|
| Fatigue | 26% | 29% | |
| Rash | 11% | 13% | |
| GI symptoms | 30% | 38% | |
| Peripheral Neuropathy | | | |
| Grade 2 | 17% | 13% | |
| Grade 3,4 | 6% | 16% | 0.003 |
| Cardiac Disorders | 6% | 6% | |
| Pneumonia | 10% | 11% | |
| DVT | 3% | 4% | |

In the PETHEMA trial, the duration of induction therapy was 24 weeks. Some 173 patients (TD:61; VcTD:54;and VBMCP/VBAD/Velcade:58) were evaluated for toxicity during induction therapy. Toxicity was assessed on an ITT basis. The total number of AEs reported in the TD, VcTD and VBMCP/VBAD/Velcade groups were 37, 36 and 44, respectively. The incidence of Grade 3 and 4 adverse events was 38%, 54% and 50% in TD, VcTD and VBMCP/VBAD/Velcade groups, respectively. Grade ≥ 3 thrombotic events were seen in 13% of patients in the TD arm. Grade ≥ peripheral neuropathy was reported in 16% of patients in the VTD arm. Treatment discontinuation due to toxicity was required

in 8 patients (TD:1; VTD:5; VBMCP/VBAD/Velcade:2). Five patients died during the induction phase (TD:3; VTD:0; VBMCP/VBAD/Velcade:2)

**Post-Marketing Experience**

No new data were submitted.

**Evaluator's Overall Conclusions on Clinical Safety**

The safety data provided in this literature based submission was limited.

In the randomised controlled trials, the adverse events that were reported by patients treated with bortezomib associated treatment regimens were in keeping with the known safety profile of bortezomib. Of the non-haematological toxicities, peripheral neuropathy continues to be a concern. The incidence of Grade 3/4 peripheral neuropathy in studies with bortezomib associated treatment regimens ranged from 8% to 16%. This incidence is in keeping with the known risk of bortezomib related peripheral neuropathy. Only one of the four studies (Study IFM 2005-01) reported on haematological toxicity. The incidence of Grade 3/4 haematological toxicity in this study was < 5%. There were no new adverse events reported.

### Clinical Summary and Conclusions

**Benefits**

The benefits of bortezomib in the sponsor's proposed usage are:

- The response rate following induction therapy with bortezomib associated treatment regimens was significantly superior to that achieved by the non bortezomib containing comparator regimens.
- The superior response rates were maintained after the first and second transplantations and subsequent consolidation therapy.
- Median progression free survival was longer in the bortezomib arm in the GIMEMA study.

**Risks**

The risks of bortezomib in the proposed usage are:

- Peripheral neuropathy continues to be a concern, albeit at previously described levels.
- There were no new adverse events reported.

**Benefit-Risk Balance**

The benefit-risk balance of bortezomib, given the proposed usage, is favourable.

**Final Recommendation Regarding Authorisation**

The application to extend the indication of Velcade (bortezomib) 3.5 mg and 1 mg Powder for Injection for the treatment of patients with previously untreated multiple myeloma, is recommended for approval, provided the responses to the questions raised with the sponsor satisfy the TGA.

# V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

# VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

## Quality

There was no requirement for a quality evaluation in a submission of this type.

## Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

## Clinical

The clinical evaluator has recommended approval of the application.

### Pharmacokinetics (PK) and pharmacodynamics (PD)

No new PK or PD data were submitted.

### Efficacy

The submission included two published Phase III studies to support efficacy of bortezomib for the expanded indication, the GIMEMA trial and the IFM 2005-01 trial. Conference abstracts for a further two Phase III trials (HOVON-65 and PETHEMA) were also included.

#### *GIMEMA trial*

The sponsor provided a copy of the published paper and a copy of the protocol for this trial. The study was a randomised, open, parallel group (x2) design trial. It included patients with previously untreated myeloma aged 18-65 years. Patients were treated with a protocol that included two administrations of HDC (melphalan 200 mg/m$^2$) each followed by autologous stem cell support (a 'double transplant').

Bortezomib was combined with thalidomide and dexamethasone (VTD) as induction and consolidation therapy. The comparator arm was the combination of thalidomide and dexamethasone (TD). The TD combination has been approved by the TGA as an induction (not consolidation) regimen for previously untreated myeloma, following consideration by ADEC at its February 2008 meeting.

The primary endpoint was the proportion of patients who achieved a complete response (CR) or near complete response (nCR) **after induction**. Multiple secondary endpoints were studied, mostly based on response rates. Progression free survival and overall survival were also studied.

For the primary endpoint of ≥ nCR **after induction** the results were as shown in Table 14 below.

**Table 14. Results for primary endpoint of ≥ nCR <u>after induction</u>,**

| | VTD (n = 236) | TD (n = 238) | p value |
|---|---|---|---|
| **CR or nCR (%)** **(95% CI)** | **31%** (25.0 – 36.8) | **11%** (7.3 – 15.1) | <0.0001 |

The results for ≥ nCR **after consolidation** were as shown in Table 15 below.

**Table 15. Results for ≥ nCR after consolidation**

| | VTD (n = 236) | TD (n = 238) | p value |
|---|---|---|---|
| **CR or nCR (%)**<br>**(95% CI)** | **62%**<br>(56.1 – 68.5) | **41%**<br>(39.1 – 51.7) | = 0.0002 |

The increase in response rate between completion of induction and completion of consolidation was comparable in both groups (~ 30%), suggesting that the addition of bortezomib to TD in consolidation provided no improvement in efficacy. The authors of the published paper concluded that the benefits of consolidation therapy needed further investigation.

PFS data were not mature as less than 50% of subjects had progressed or died. However there was a statistically significant improvement in PFS in the bortezomib arm (hazard ratio = 0.63; 95%CI 0.45 – 0.88; p = 0.0061). PFS at 3 years was 68% in the VTD arm and 56% in the TD arm (p = 0057).There was no significant difference in overall survival, although these data were also not mature.

Addition of bortezomib to the TD induction regimen did not adversely affect subsequent stem cell mobilisation.

### *IFM-2005 trial*

The sponsor provided a copy of the published paper, a copy of the protocol and the statistical analysis plan for this trial. The study was a randomised, open, parallel group (x4) design trial. It included patients with previously untreated myeloma aged ≤ 65 years. Patients were treated with a protocol that included one or two administration of HDC (melphalan 200 mg/m$^2$) each followed by autologous stem cell support.

For **induction,** patients were randomised to receive a standard regimen (vincristine + Adriamycin + dexamethasone [VAD]) or a combination of bortezomib with dexamethasone (VD). Patients were also randomised to receive **consolidation** treatment or no consolidation treatment, prior to HDC. The consolidation regimen used (DCEP) did not include bortezomib.

The primary endpoint was the proportion of patients who achieved a complete response (CR) or near complete response (nCR) **after induction**. Progression free survival and overall survival were also studied.

For the primary endpoint of ≥ nCR after induction, the results were as shown in Table 16 below.

**Table 16. Results for the primary endpoint of ≥ nCR after induction**

| | VD (n = 240) | VAD (n = 242) | p value |
|---|---|---|---|
| **CR or nCR (%)**<br>**(95% CI)** | **14.8 %**<br>(CI not stated) | **6.4 %**<br>(CI not stated) | = 0.004 |

There was no significant difference in PFS or overall survival.

Compared with VAD, the use of bortezomib in the VD induction regimen did not adversely affect subsequent stem cell mobilisation.

***Other studies***

The results of the HOVON-65 and PETHEMA trials were only available in abstract format and hence cannot be relied upon as conclusive evidence of efficacy. The available results indicated:

- In HOVON-65, a combination of bortezomib + Adriamycin + dexamethasone (PAD) as induction gave superior response rates to VAD induction;
- In PETHEMA, a combination of bortezomib + thalidomide + dexamethasone (VcTD) as induction gave superior CR rates to TD induction.

The current Australian submission included a large number of Phase 1 and 2 studies in which bortezomib was combined with a variety of agents. As these studies did not compare bortezomib containing regimens with standard therapy, they provide no meaningful additional evidence of efficacy.

**Safety**

As is usual with published versions of clinical trials, only brief details of safety were reported.

In the GIMEMA study, the addition of bortezomib to TD resulted in an increase in the incidence of Grade 3 or 4 adverse events (56% versus 33%) but no increase in serious adverse events (13% versus 13%) or discontinuations due to adverse events (4% versus 3%). With respect to individual toxicities, the bortezomib arm was associated with increased incidences of constipation, other GIT adverse events, skin rash, neuropathy and oedema. This pattern of individual toxicities is consistent with that previously observed with bortezomib.

In the IFM-2005 study, when compared to the standard VAD regimen, the VD (bortezomib) regimen was associated with a lower incidence of serious adverse events (27.2% versus 33.9%) and deaths related to toxicity (0 versus 2.9%). With respect to individual toxicities, the bortezomib arm was associated with increased incidences of thrombocytopaenia, fatigue, rash and peripheral neuropathy. Again, this pattern of individual toxicities is consistent with that previously observed with bortezomib.

In the HOVON-65 study, the PAD regimen was associated with some increase in overall toxicity compared to the standard VAD regimen.

## Risk Management Plan

An RMP was not required to be submitted with the current application.

## Risk-Benefit Analysis

### Delegate Considerations

**1. Overall risk-benefit**

*Efficacy issues*: Both of the published studies included in the current Australian submission used response rate as the primary endpoint. Achievement of a complete response (CR) is believed to correlate with improved survival outcomes in myeloma. However, the TGA has adopted an EMA guideline which sets out appropriate efficacy

endpoints for Phase III studies in haematological malignancies[12]. It suggests (section 3.3) that PFS is the appropriate endpoint for Phase III studies in myeloma. The following points are brought to the ACPM's attention:

- In the GIMEMA study, there was a significant benefit in terms of PFS when bortezomib was added to TD. However the PFS data were not mature and values for median PFS could not be estimated;
- In the IFM-2005 study, there was no significant difference in PFS between the bortezomib (VD) and VAD arms, suggesting that the VD combination has comparable efficacy to an established regimen. However, the trial was not designed to establish non inferiority;

*Safety issues*: The data provided from the Phase III studies on the safety of bortezomib in combination in the HDC eligible population were sparse. Approval of the new indication would require some degree of assumption that the safety profile of the drug when used in the new population and in combination with other agents is unlikely to be different to that previously observed. On the other hand, the limited data from the IFM-2005 study suggest that there may be some safety advantages with the VD regimen compared to the standard VAD regimen.

*Overall risk-benefit*: The studies in the current Australian submission were investigator initiated and only available in the form of published papers. As a result, the evidence for both efficacy and safety falls short of that usually required, for example by EMA guidelines. The drug has been approved in Australia since 2006 and in major foreign markets since 2005. Hence, there is significant experience with its use in myeloma patients. In addition, use of the drug in the setting of patients undergoing HDC with autologous stem cell support will be confined to specialised units. On balance, the Delegate considered that there is sufficient evidence to conclude that the efficacy benefits of bortezomib in the new population will outweigh its toxicity and the Delegate proposed to approve the application.

## 2. Indication

The currently approved first line indication is:

> *"Velcade in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy".*

The proposed new first line indication is:

> *"Velcade, as part of combination therapy is indicated for the treatment of patients with previously untreated multiple myeloma."*

The proposed new indication incorporates a number of new uses for bortezomib, for example:

- Use, in combination with agents other than melphalan and steroids, in patients who are not candidates for high dose chemotherapy. No new controlled studies in the non transplant eligible setting have been submitted to support such use.

[12] EMA/CHMP/EWP/520088/2008 Appendix 2 to the Guideline on the evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3) on Confirmatory studies in Haematological Malignancies (http://www.tga.gov.au/pdf/euguide/chmp52008808enfin.pdf)

- Use as consolidation treatment (after induction). The GIMEMA study was the only randomised controlled trial submitted that examined use of bortezomib as part of a consolidation regimen. As indicated above, the study did not support such use.
- Use as maintenance therapy. No controlled studies have been submitted to support such use.

In light of the above it could be argued that the indications that should be approved are:

> *"Velcade in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy".*
>
> *"Velcade, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients with previously untreated multiple myeloma."*

The sponsor was asked to comment on this proposed restriction and their response is included below. As pointed out by the sponsor in their response, the use of bortezomib in combination with many other agents, in all stages of myeloma, is supported by various current clinical practice guidelines published by expert bodies.

It is also noted that the FDA has granted the product a very broad indication ("the treatment of patients with multiple myeloma").

If the ACPM agrees that the application should be approved, advice is sought as to the appropriate wording of the indication.

The Delegate proposed to approve the application, at least for the limited indication outlined above. The advice of the ACPM was requested.

**Response from Sponsor**

The Sponsor disagreed with the Delegate's recommendation for the reasons set below.

The treatment of MM is evolving from a backbone of induction followed by transplant to further treatment after transplant with either short course drug exposure (consolidation) or longer courses until disease progression (maintenance).

The important outcome to studies which added further drug after transplant is that there is an increase in Complete Responses (CR). It has also been established that CR state has a better outcome than lower responses. The VTD versus TD study shows an increased CR in the VTD group compared to the TD during the induction phase.

This higher CR is maintained post transplant and post consolidation. The CR is only part of the beneficial efficacy end points. PFS was significantly improved with VTD treatment compared to the TD, although the contribution of individual phases remains to be fully elucidated. There are other equally important efficacy parameters which are contributory to both PFS and OS such as prolonged duration of response, treatment free intervals which could have been impacted by the VTD treatment regimen. It should also be noted that limiting approval of VTD for induction only is rather incomplete as the study for its basis of approval has the consolidation component and all the efficacy results under discussion are indeed due to both components of treatment. There is a potential of negatively impacting the perceived substantial improvement in PFS observed in the GIMEMA study by partial implementation.

What is more important, however, is the demonstration by other recent studies such as the final survival analysis of the VISTA study, that optimal treatment needs to be given on

first line as that advantage is maintained regardless of any relapse treatment regimen. Further, mature data from other studies as such as the HOVON have shown that post transplant (consolidation) treatment with Velcade has both PFS and survival advantage compared to post transplant treatment with thalidomide.

One of the benefits of Velcade as a therapy in newly diagnosed MM patients is its rapid action. This is particularly important clinically for newly diagnosed patients (both transplant eligible and non transplant eligible) where the initial goal of therapy is to rapidly reduce tumour burden and restore organ function quickly (for example by preventing renal damage or further bone damage). For patients who are renally compromised (and otherwise not able to proceed to ASCT), using Velcade upfront may enable this group to then recover sufficient renal function to proceed to ASCT which is currently accepted as part of the standard of care for newly diagnosed patients fit enough to undergo this procedure. Also by restricting the NTE to a combination of melphalan and prednisone only, the TGA does not take into consideration some groups that are not tolerant of melphalan, such as renally impaired patients who are not suitable for HDC.

It is envisaged that Velcade is and will be used over the wide spectrum MM treatment, without splitting it into phases. This point was recognised by the clinical evaluator as clearly shown in the Clinical Evaluation Report where a recommendation was made to approve this submission for the broad indication originally proposed by the sponsor.

The sponsor, therefore, requests that the proposed broad indication be retained.

**Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents advised the following:

**Efficacy**

The ACPM noted that the studies submitted were only available as published papers. As a result, the evidence for both efficacy and safety falls short of that usually expected in EMA guidelines[12]. Both these studies used response rate as the primary endpoint which is believed to correlate with improved survival outcomes in myeloma; however, the committee noted that the TGA adopted EMA guideline suggests that Progression Free Survival is the appropriate endpoint for Phase III studies in myeloma.

In the GIMEMA study, there was a significant benefit in terms of PFS when bortezomib was added to TD treatment (thalidomide + dexamethasone) as part of induction therapy prior to high dose chemotherapy with autologous stem cell rescue; however, the data were not mature. The IFM-2005 study suggested that the VD combination (bortezomib with dexamethasone as induction therapy) has comparable efficacy to an established regimen. The trial was not, however, designed to establish non inferiority.

The indication, as proposed by the sponsor, was a considerable expansion of that currently approved. It included use in any combination in the non transplant eligible population; however, no new controlled studies in the non transplant eligible setting have been submitted. It also included use as consolidation or maintenance therapy. The GIMEMA study examined use of bortezomib as part of a consolidation regimen (after induction) but did not support this use.

**Safety**

The data provided from the Phase III studies on the safety of bortezomib in combination in the High Dose Chemotherapy (HDC) eligible population were sparse. On the other hand,

bortezomib has been approved in Australia since 2006 and in major foreign markets since 2005; hence there is significant experience with its use in myeloma patients.

The limited trial data submitted suggest that there may be some safety advantages with the VD induction regimen (bortezomib + dexamethasone) trialled compared to the standard VAD (vincristine + adriamycin + dexamethasone) regimen.

The use of bortezomib in the setting of patients undergoing HDC with autologous stem cell rescue will be confined to specialised units, providing a further level of monitoring and safety.

The ACPM supported the proposed amendments to the Product Information (PI) with the addition of a clear statement on lack of data in patients over 65 years of age. It was the view of the committee that the age limit should be added to the indication.

The first line indications that are supported are:

> *Velcade in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy.*
>
> *Velcade, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.*

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of safety and efficacy provided for bortezomib (Velcade) would support the safe and effective use of this product.

### Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Velcade containing bortezomib for the new indication:

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

# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

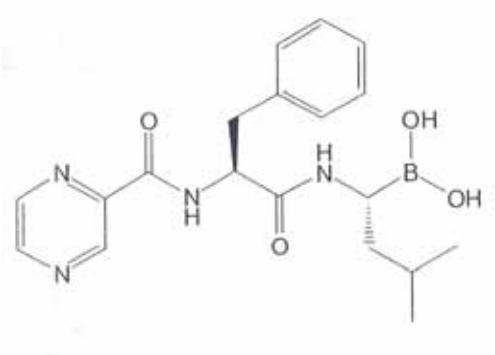
# VELCADE®

## PRODUCT INFORMATION

## NAME OF THE MEDICINE

Bortezomib

Bortezomib has the following chemical structure:




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

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

## DESCRIPTION

VELCADE (bortezomib) is an antineoplastic agent for intravenous injection (IV) use only. Each single dose vial contains 3.5mg of bortezomib as a sterile lyophilised powder. Inactive ingredients: 35mg mannitol and nitrogen qs.

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.

# PHARMACOLOGY

## Pharmacodynamics

*Mechanism of Action*

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

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

## Pharmacokinetics

Following intravenous bolus administration of a 1.0 mg/$m^2$ and 1.3 mg/$m^2$ dose to eleven patients with multiple myeloma, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/mL respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106ng/mL for the 1.0mg/$m^2$ dose and 89 to 120ng/mL for the 1.3mg/$m^2$ dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1.0mg/$m^2$ and 1.3mg/$m^2$, respectively, and ranged from 15 to 32 L/h following subsequent doses of 1.0mg/$m^2$ and 1.3mg/$m^2$, respectively. The mean distribution volume of bortezomib ranged from 1659 litres to 3294 litres **(**489 to 1884L/$m^2$**)** following single- or repeat-dose administration of 1.0mg/$m^2$ or 1.3mg/$m^2$ to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues.

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

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

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

***Renal Impairment:*** A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL≥60 mL/min/1.73 $m^2$, n=12), Mild (CrCL=40-59 mL/min/1.73 $m^2$, n=10), Moderate (CrCL=20-39 mL/min/1.73 $m^2$, n=9), and Severe (CrCL < 20 mL/min/1.73 $m^2$, n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/$m^2$ of bortezomib twice weekly. Clearance of bortezomib was comparable among all the groups. However, the number of patients with severe renal impairment was insufficient to allow reliable conclusions regarding this group (see **PRECAUTIONS**).

***Hepatic Impairment:*** formal studies in patients with severely impaired hepatic function have not been conducted to date; consequently caution is recommended when administering bortezomib to these classes of patients (see **PRECAUTIONS**).

# CLINICAL TRIALS

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

## Previously Untreated Multiple Myeloma

### *Transplant Eligible*

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

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

Patients randomized to Vc-TD arm achieved significantly higher rates of complete plus near complete response and very good partial response or better, compared to the thalidomide-dexamethasone arm following induction treatment. This difference was maintained following both transplant and consolidation therapy. Response rates are presented in Table 1.

**Table 1: Summary of Response Rates by IMWG criteria in the GIMEMA study**

| Response Rate n (%) | Vc-TD n=236 | TD n=238 | *p*-value |
|---|---|---|---|
| **Post-induction Therapy*** | | | |
| CR | 44 (19) | 11 (5) | <0.0001 |
| CR+nCR** | 73 (31) | 27 (11) | <0.0001 |
| ≥VGPR | 146 (62) | 66 (28) | <0.0001 |
| ≥PR | 220 (93) | 187 (79) | <0.0001 |
| MR/SD | 16 (7) | 39 (16) | 0.0011 |
| PD | 0 | 12 (5) | 0.0005 |
| **Post-first ASCT** | | | |
| CR | 89 (38) | 54 (23) | 0.0004 |
| CR+nCR | 123 (52) | 74 (31) | <0.0001 |
| ≥VGPR | 186 (79) | 137 (58) | <0.0001 |
| ≥PR | 220 (93) | 201 (84) | 0.0025 |
| MR/SD | 15 (6) | 20 (8) | 0.3941 |
| PD | 1 (0) | 17 (7) | 0.0001 |
| **Post-second ASCT** | | | |
| CR | 98 (42) | 72 (30) | 0.0105 |
| CR+nCR | 130 (55) | 98 (41) | 0.0024 |
| ≥VGPR | 193 (82) | 152 (64) | <0.0001 |
| ≥PR | 220 (93) | 199 (84) | 0.0011 |
| MR/SD | 14 (6) | 19 (8) | 0.3804 |
| PD | 2 (1) | 20 (8) | 0.0001 |
| **Post-consolidation** | | | |
| CR | 116 (49) | 82 (34) | 0.0012 |
| CR+nCR | 147 (62) | 108 (45) | 0.0002 |
| ≥VGPR | 201 (85) | 162 (68) | <0.0001 |
| ≥PR | 218 (92) | 201 (84) | 0.0071 |
| MR/SD | 12 (5) | 16 (7) | 0.4495 |

| | | | |
|---|---|---|---|
| PD | 6 (3) | 21 (9) | 0.0032 |
| **Best overall response** | | | |
| CR | 136 (58) | 97 (41) | 0.0001 |
| CR+nCR | 168 (71) | 128 (54) | <0.0001 |
| ≥VGPR | 210 (89) | 175 (73.5) | <0.0001 |
| ≥PR | 227 (96) | 212 (89) | 0.0074 |

* Similar differences in post-induction response rates were reported by study investigators (CR+nCR: 32% vs. 13%, *p*<0.0001). Differences in RR following transplantation and consolidation by investigator assessment were also similar to those centrally assessed.
** These significant differences in CR+nCR rates between arms were maintained following cyclophosphamide to collect peripheral blood stem cells (42% vs 21%, *p*<0.0001).

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

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

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

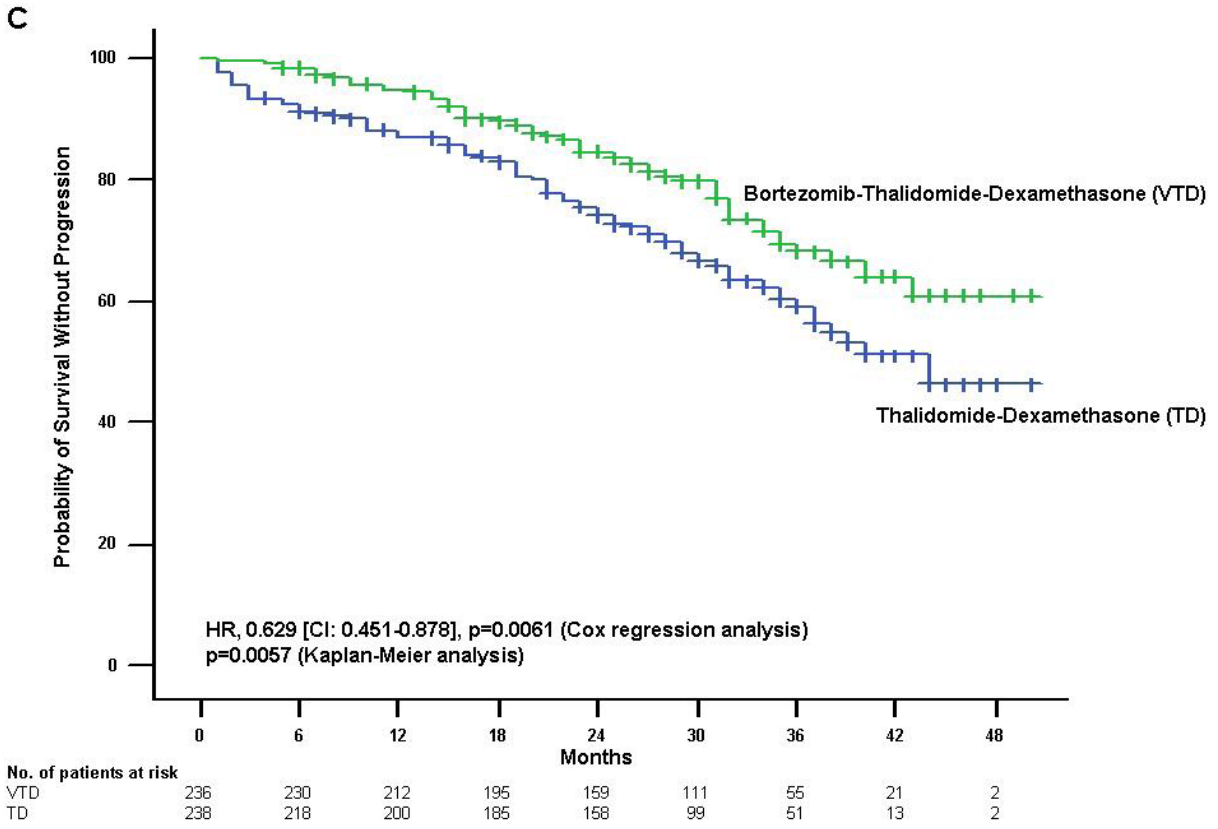
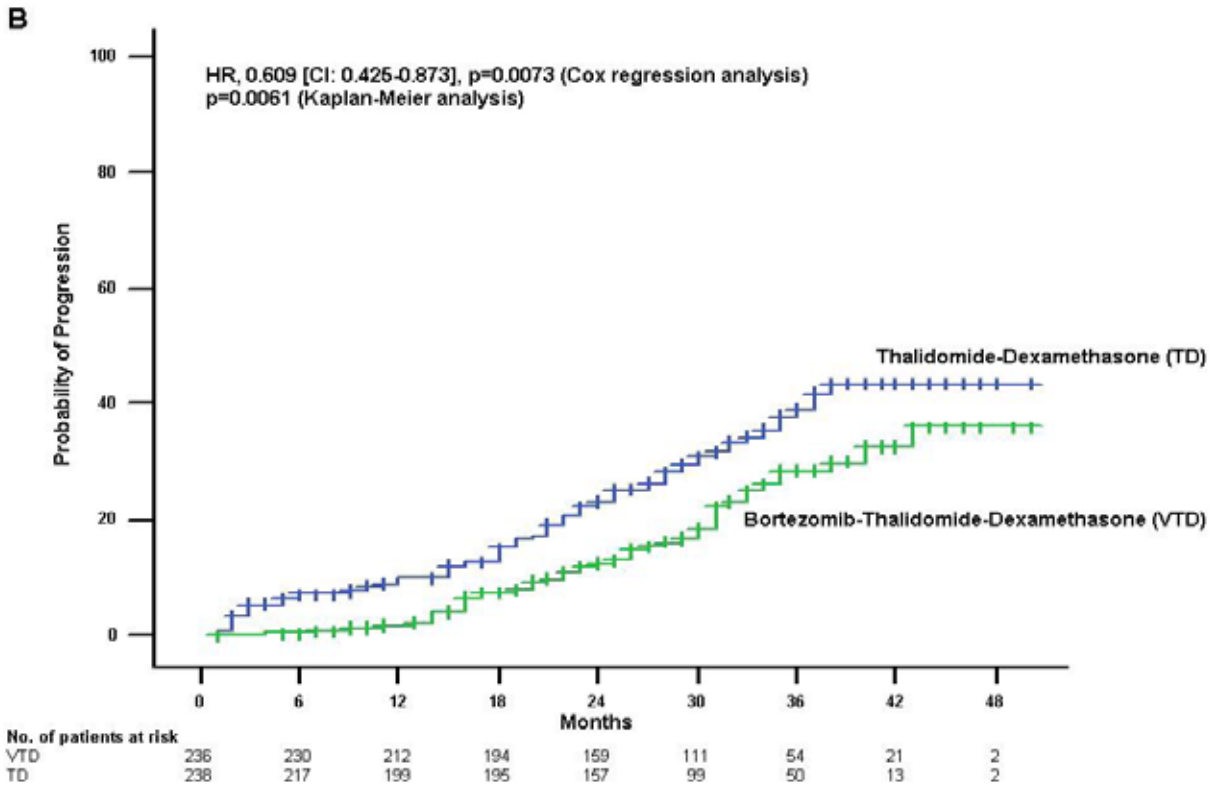


**Figure 2: Time to Disease Progression**
**(Study GIMEMA: All Randomised Subjects Analysis Set)**




The IFM-2005, Phase III, randomised (1:1:1:1), multi-centre, open-label study was conducted to compare the efficacy and safety of VELCADE-dexamethasone (Vc-Dex) and vincristine-doxorubicin-dexamethasone (VAD) as induction therapy prior to HDT-ASCT, and to evaluate the impact of post-induction consolidation therapy. Patients in this study were randomised to receive VAD plus no consolidation (arm A1), VAD plus dexamethasone, cyclophosphamide, etoposide, cis-platin (DCEP) consolidation (arm A2), Vc-Dex plus no consolidation (arm B1), or Vc-Dex plus DCEP consolidation (arm B2).

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

Patients randomized to the Vc-Dex arm achieved significantly higher rates of complete plus near complete response and very good partial response or better, compared to the VAD arm following induction treatment. Based on an intention to treat analysis, response rates were similar regardless of whether patients received DCEP consolidation or not. Efficacy results are presented in Table 2:

**Table 2: Response to induction therapy (overall) in the IFM2005 study***

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

A total of 184/218 (84.4%) and 197/223 (88.3%) evaluable patients who received VAD and Vc-Dex induction, respectively, underwent autologus stem cell transplantation. The number of patients who received a second transplantation was 41 (20.8%) in the Vc-Dex arm, compared to 50 (27.2%) for patients in the VAD arm. Post-transplant response rates are shown in Table 3.

**Table 3: Response rates post-transplantation***

| | VAD (A1+A2) N=218 | Vc-Dex (B1+B2) N=223 | *p*-value |
|---|---|---|---|
| **Response to first transplant** | | | |
| ORR (≥PR), n (%) | 168 (77.1) | 179 (80.3) | 0.401 |
| ≥VGPR | 81 (37.2) | 121 (54.3) | <0.001 |
| CR/nCR | 40 (18.4) | 78 (35.0) | <0.001 |
| CR | 19 (8.7) | 36 (16.1) | 0.016 |
| MR+SD+PD | 8 (3.7) | 6 (2.7) | |
| Death | 2 (0.9) | 1 (0.5) | |
| No transplantation | 34 (15.6) | 26 (11.7) | |
| **Overall, including second transplantation** | | | |
| ≥VGPR | 102 (46.7) | 151 (67.7) | <0.001 |
| CR/nCR | 49 (22.5) | 88 (39.5) | <0.001 |

* All response assessments were confirmed by an Independent Review Committee.
CR: complete response; MR: minimal response; nCR: near-complete response; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease; VGPR: very good partial response.

In addition, the median PFS was 29.7 months among patients who received VAD versus 36.0 months among patients who received Vc-Dex induction, with 128 (52.9%) of 242 and 110 (45.8%) of 240 patients, respectively, having progressed ($p = 0.064$, or $p = 0.057$ if adjusted for initial stratification factors) after median follow-up of 31.2 months.

### *Non-Transplant Eligible*

The VISTA study is a prospective phase III, international, randomized (1:1), open-label clinical study of 682 patients, conducted to determine whether VELCADE (1.3 mg/m$^2$) in combination with melphalan (9 mg/m$^2$) and prednisone (60 mg/m$^2$) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m$^2$) and prednisone (60 mg/m$^2$) in patients with previously untreated multiple myeloma 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 4.

**Table 4: Summary of Baseline Patient and Disease Characteristics in the VISTA Study**

| Patient Characteristics | VcMP N=344 | MP N=338 |
|---|---|---|
| Median age in years (range) | 71.0 (57, 90) | 71.0 (48, 91) |
| Gender: male/female | 51% / 49% | 49% / 51% |
| Race: Caucasian/asian/black/other | 88% / 10% / 1% / 1% | 87% / 11% / 2% / 0% |
| Karnofsky performance status score ≤70 | 35% | 33% |
| Hemoglobin <100 g/L | 37% | 36% |
| Platelet count <75 x $10^9$/L | <1% | 1% |
| **Disease Characteristics** | | |
| Type of myeloma (%): IgG/IgA/Light chain | 64% / 24% / 8% | 62% / 26% / 8% |
| Median $\beta_2$-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 = VELCADE + 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 5 and Figure 1) was 16.3 months. Median follow-up in the last survival analysis (Figure 2) was 36.7 months. Median overall survival in the MP arm was 43.1 months and was not reached in the VcMP arm. Fifty percent of subjects in the MP arm subsequently received VELCADE.

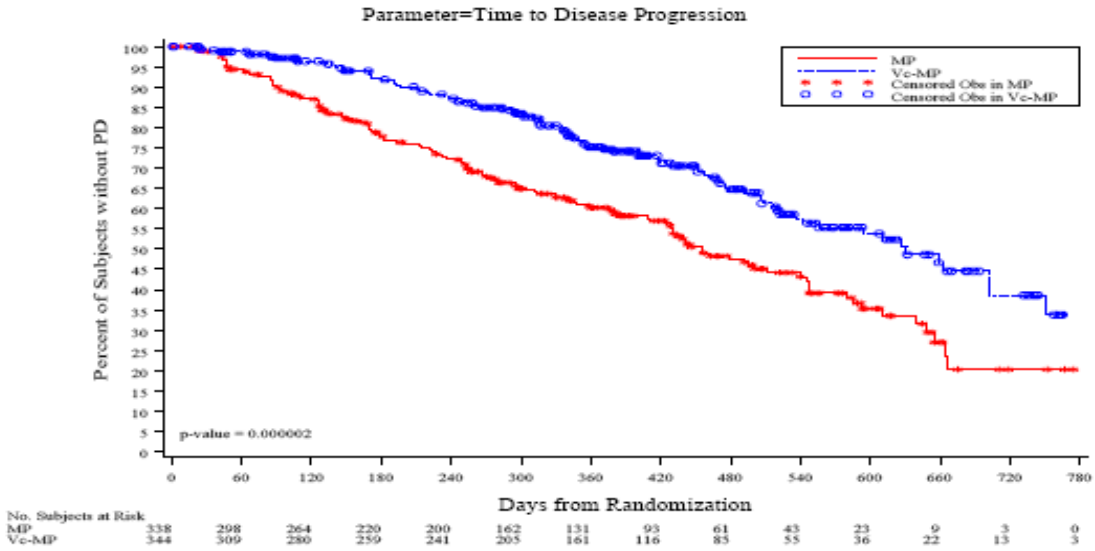
**Table 5: Summary of Efficacy Analyses in the VISTA study**

| **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-hazard model adjusted for stratification factors: beta2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP
[c] p-value based on the stratified log-rank test adjusted for stratification factors: beta2-microglobulin, albumin, and region
[d] p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors
[e] Response population includes patients who had measurable disease at baseline
[f] EBMT criteria
[g] All randomized patients with secretory disease
NE: Not estimable

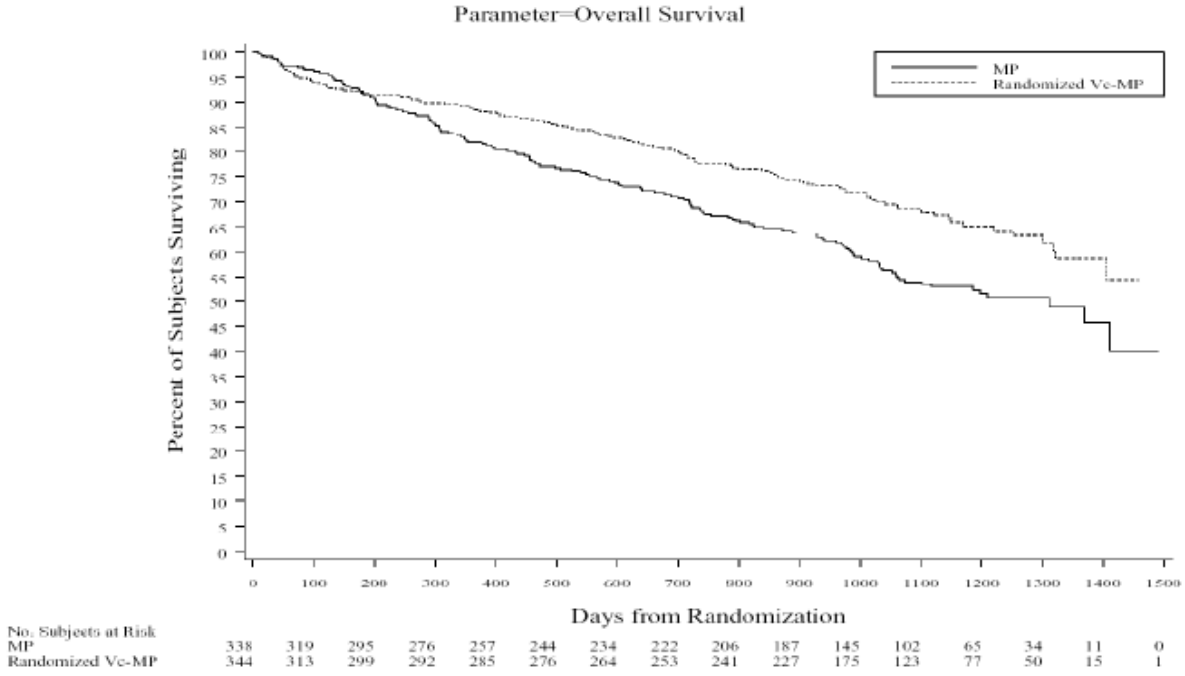
The time to progression (TTP) was significantly longer on the VELCADE arm (see Figure 3)

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




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

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



## Relapsed / Refractory Multiple Myeloma

The safety and efficacy of VELCADE were evaluated in 2 studies at the recommended dose of 1.3 mg/m$^2$: The APEX study - a phase III randomised, stratified, open-label, comparative study, versus Dexamethasone (Dex), of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy, and a phase II single-arm study of 202 patients with relapsed and refractory multiple myeloma, who had received at least 2 prior lines of treatment and who were progressing on their most recent treatment (see Tables 6 and 7).

**Table 6: Dosing regimens in the APEX and Phase II studies**

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

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

**Table 7: Patient characteristics in the Phase II* and APEX Studies**

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

*Based on number of patients with baseline data available

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

**APEX Study (Phase III)**

In the APEX study described above, patients considered to be refractory to prior high-dose dexamethasone were excluded as were those with baseline grade ≥ 2 peripheral neuropathy or platelet counts <50,000/µL. A total of 627 patients were evaluable for response. Stratification factors were based on the number of lines of prior therapy the patient had previously received (1 previous line versus more than 1 line of therapy), time of progression relative to prior treatment (progression during or within 6 months of stopping their most recent therapy versus relapse >6 months after receiving their most recent therapy), and screening $\beta_2$-microglobulin levels (≤ 2.5 mg/L versus >2.5 mg/L).

Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients randomized to dexamethasone were offered VELCADE, regardless of disease status. At this time of study termination, a final statistical analysis was performed. Due to this early termination of the study, the median duration of follow-up for surviving patients (n=534) is limited to 8.3 months. The time to event analyses and response rates from the APEX trial are presented in Table 8.

**Table 8: Summary of Efficacy Analyses in the APEX Study**

| | **All Patients** | | **1 Prior Line of Therapy** | | **>1 Prior Line of Therapy** | |
|---|---|---|---|---|---|---|
| | **VELCADE** | **Dex** | **VELCADE** | **Dex** | **VECADE** | **Dex** |
| **Efficacy Endpoint** | **n=333** | **n=336** | **n=132** | **n=119** | **n=200** | **n=217** |
| **Time to Progression** – Events n (%) | 147(44) | 196(58) | 55(42) | 64(54) | 92(46) | 132(61) |
| Median[a] (95% CI) | 6.2 mo (4.9, 6.9) | 3.5 mo (2.9, 4.2) | 7.0 (6.2, 8.8) | 5.6 (3.4, 6.3) | 4.9 (4.2, 6.3) | 2.9 (2.8, 3.5) |
| Hazard ratio[b] (95% CI) | 0.55 (0.44, 0.69) | | 0.55 (0.38, 0.81) | | 0.54 (0.41, 0.72) | |
| p-value[c] | <0.0001 | | 0.0019 | | <0.0001 | |
| **Overall survival** Events (deaths) n (%) | 51(15) | 84(25) | 12(9) | 24(20) | 39(20) | 60(28) |
| Hazard ratio[b] (95% CI) | 0.57 (0.40, 0.81) | | 0.39 (0.19, 0.81) | | 0.65 (0.43, 0.97) | |
| p-value[c, d] | <0.05 | | <0.05 | | <0.05 | |
| **Response Rate** population[e] n=627 | n=315 | n=312 | n=128 | n=110 | n=187 | n=202 |
| CR[f] n(%) | 20(6) | 2(<1) | 8(6) | 2(2) | 12(6) | 0(0) |
| PR[f] n(%) | 101(32) | 54(17) | 49(38) | 27(25) | 52(28) | 27(13) |
| nCR[f,g] n(%) | 21(7) | 3(<1) | 8(6) | 2(2) | 13(7) | 1(<1) |
| CR + PR[f] n(%) | 121(38) | 56(18) | 57(45) | 29(26) | 64(34) | 27(13) |
| p-value[h] | <0.0001 | | 0.0035 | | <0.0001 | |
| **Median Response Duration** | | | | | | |
| CR[f] | 9.9 mo | NE[i] | 9.9 mo | NE | 6.3 mo | NA[j] |
| nCR[f] | 11.5 mo | 9.2 mo | NE | NE | 11.5 mo | 9.2 mo |
| CR + PR[f] | 8.0 mo | 5.6 mo | 8.1 mo | 6.2 mo | 7.8 mo | 4.1 mo |

[a] Kaplan-Meier estimate
[b] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for VELCADE.
[c] p-value based on the stratified log-rank test including randomisation stratification factors.
[d] Precise p-value cannot be rendered
[e] Response population includes patients who had measurable disease at baseline and received at least 1 dose of study dose
[f] EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria, nCR in the PR category.
[g] In 2 patients, the IF was unknown.
[h] p-value for Response Rate (CR + PR) from the Cochrane-Mantel-Haenszel chi-square test adjusted for the stratification factors;
[i] Not Estimable.
[j] Not Applicable, no patients in category.

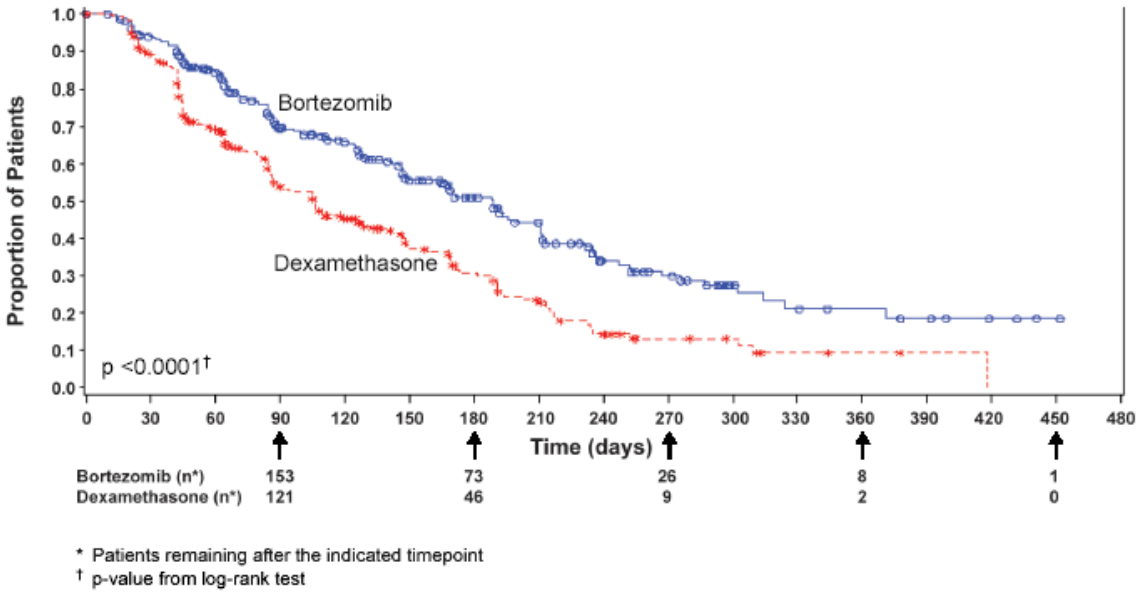
For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the dexamethasone arm.

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

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

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

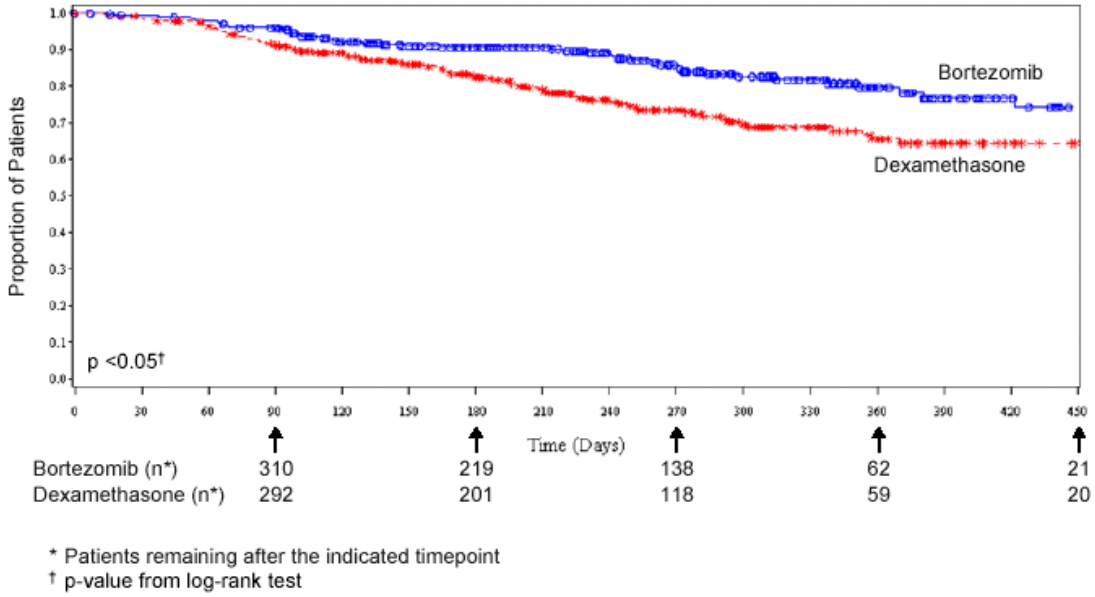
**Figure 5: Time to progression**
**Bortezomib vs Dexamethasone**




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

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

**Figure 6: Overall Survival**
**Bortezomib vs Dexamethasone**




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

## Phase II studies

The safety and efficacy of VELCADE were evaluated in an open-label, single-arm, multi-centre study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Dosing regimens and baseline patient and disease characteristics are summarised in Table 6 and Table 7. The study employed dose modifications for toxicity (see **DOSAGE AND ADMINISTRATION**). Responses to VELCADE alone in the phase II study are shown in Table 9.

In general, patients who had confirmed Complete Response received 2 additional cycles of VELCADE treatment beyond confirmation. The median time to response was 38 days (range 30 to 127 days). The median survival of all patients enrolled was 16 months (range <1 to 18+ months). The response rate to VELCADE was independent of the number and types of prior therapies.

**Table 9: Summary of disease outcomes in Phase II study**

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

[1]**Complete Response** required 100% disappearance of the original monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.
[2]**Partial Response** required ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.
[3]**Clinical remission (SWOG)** required ≥ 75% reduction in serum myeloma protein and/or ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

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

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

# INDICATIONS

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

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

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

# CONTRAINDICATIONS

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

# PRECAUTIONS

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

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

**Peripheral Neuropathy**

VELCADE treatment causes a peripheral neuropathy 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 VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperaesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of VELCADE (see **DOSAGE AND 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 III study. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥ Grade 3 peripheral neuropathy in the phase II studies (see **ADVERSE 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.

**Hypotension**

Patients developing orthostatic hypotension on VELCADE did not have evidence of orthostatic hypotension prior to treatment with VELCADE. 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 VELCADE.

In phase II and III studies, the incidence of hypotension (postural, orthostatic and hypotension not otherwise specified) was 11% to 12%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope receiving medications known to be associated with hypotension and with patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids and/or sympathomimetics (see **ADVERSE 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 III study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the VELCADE and dexamethasone groups, 5% and 4%, respectively. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

**Pulmonary Disorders**

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving VELCADE. Some of these events have been fatal. A higher proportion of these events have been reported in Japan. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients treated appropriately.

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

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

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

**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.

**Amyloidosis**

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

**Laboratory Tests**

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

## Thrombocytopenia

VELCADE treatment is associated with thrombocytopenia (see **ADVERSE EFFECTS**). Platelet counts were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. On average, the pattern of platelet count decrease and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pre-treatment platelet count is shown in Table 10 for the phase III study. In the phase III study, the incidence of significant bleeding events (≥ Grade 3) was similar on both the VELCADE (4%) and dexamethasone (5%) arms. Platelet counts should be monitored prior to each dose of VELCADE. VELCADE therapy should be held when the platelet count is <25,000/μL and reinitiated at a reduced dose after resolution (see **DOSAGE AND ADMINISTRATION** and **ADVERSE EFFECTS**). Transfusions may be used at the discretion of the physician. There have been reports of gastrointestinal and intracerebral haemorrhage in association with VELCADE.

**Table 10: The Severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the APEX study**

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

*A baseline platelet count of 50,000/μL was required for study eligibility.

**Data for one patient was missing at baseline

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

## Gastrointestinal Adverse Events

VELCADE treatment can cause nausea, diarrhoea, constipation and vomiting (see **ADVERSE EFFECTS**) sometimes requiring use of antiemetics and antidiarrhoeals. Fluid and electrolyte replacement should be administered to prevent dehydration. Since patients receiving VELCADE 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 VELCADE is a cytotoxic agent and can rapidly kill malignant cells the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

## Hepatic Events

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

## Patients with Hepatic Impairment

Patients with moderate and severe hepatic impairment should be treated with caution at reduced starting doses of VELCADE and closely monitored for toxicities. 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 to 1.3 $mg/m^2$ (see Table 19 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.

**Patients with Renal Impairment**

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

**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 VELCADE may affect male and female fertility.

**Use in Pregnancy**

**Category C**

Women of child bearing potential should avoid becoming pregnant while being treated with VELCADE. 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 VELCADE 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 VELCADE, women should be advised against breast-feeding while being treated with VELCADE.

**Paediatric Use**

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

**Carcinogenicity**

Carcinogenicity studies have not been conducted with bortezomib.

**Effects on Laboratory Tests**

None known.

**Effect on Ability to Drive or Operate Machinery**

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

# INTERACTIONS WITH OTHER MEDICINES

*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 metabolizer phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A inhibitor, 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, there was no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients.

The concomitant use of VELCADE 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.

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

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

# ADVERSE EFFECTS

## Adverse events

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

*Results from the GIMEMA and IFM2005 studies*

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

**Table 11: Adverse events (Grade III/IV) following induction in randomised, controlled studies GIMEMA and IFM2005**

| Adverse event, n (%) | GIMEMA | | IFM2005 | |
|---|---|---|---|---|
| | VcTD n=236 | TD n=238 | VcD n=239 | VAD n=239 |
| Any adverse event | nr | nr | 231 (96.7)* | 219 (91.6)* |
| Any serious adverse event | 31 (13.1) | 30 (12.6) | 65 (27.2) | 81 (33.9) |
| Any grade 3 or 4 adverse event | 132 (55.9) | 79 (33.1) | 112 (46.9) | 110 (46.0) |
| **Any grade 3 or 4 non-haematologic adverse event** | 120 (50.8) | 73 (30.6) | nr | nr |
| Skin rash | 24 (10.1) | 4 (1.6) | nr | nr |
| Peripheral neuropathy | 23 (9.7) | 5 (2.1) | 17 (7.1) | 5 (2.1) |

| | | | | |
|---|---|---|---|---|
| Deep vein thrombosis | 8 (3.3) | 12 (5.0) | nr | nr |
| Constipation | 10 (4.2) | 7 (2.9) | nr | nr |
| Infections | nr | nr | 21 (8.8) | 29 (12.1) |
| Infections excluding herpes zoster | 7 (2.9) | 11 (4.6) | nr | nr |
| Herpes zoster (all grades) | nr | nr | 22 (9.2) | 5 (2.1) |
| Gastrointestinal events (excluding constipation where individually reported) | 5 (2.1) | 1 (0.4) | nr | nr |
| Cardiac toxicity | 5 (2.1) | 5 (2.1) | nr | nr |
| Liver toxicity | 4 (1.6) | 7 (2.9) | nr | nr |
| Fatigue (all grades) | nr | nr | 68 (28.5) | 50 (20.9) |
| Oedema (all grades) | 25 (11) | 13 (5) | | |
| **Any grade 3 or 4 haematologic adverse event** | nr | nr | nr | nr |
| Anaemia | nr | nr | 10 (4.2)* | 21 (8.8)* |
| Neutropaenia | nr | nr | 12 (5.0)* | 24 (10.0)* |
| Thrombocytopenia | nr | nr | 7 (2.9) | 3 (1.3) |
| Thrombosis | nr | nr | 4 (1.7)* | 13 (5.4)* |
| Discontinued during or after induction therapy | 13 (5.5) | 26 (10.9) | 44 (18.4) | 32 (13.4) |
| Adverse event leading to death | 1 (0.4) | 0 (0) | 0 (0)* | 7 (2.9)* |

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

During consolidation therapy of the GIMEMA study, grade 3-4 adverse events were similar to those reported during induction, although rates were much lower. Notably, the rate of grade 3-4 peripheral neuropathy was 1.2% with VcTD consolidation compared to 0% with TD consolidation.

*Results from the VISTA study*

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

**Table 12: Treatment Emergent Drug-Related Adverse Events reported in ≥ 10% of patients treated with VELCADE 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) | 77 ( 23) | 42 ( 12) |
| Anaemia | 109 ( 32) | 41 ( 12) | 4 ( 1) | 156 ( 46) | 61 ( 18) | 18 ( 5) |
| Leukopenia | 108 ( 32) | 64 ( 19) | 8 ( 2) | 93 ( 28) | 53 ( 16) | 11 ( 3) |
| Lymphopenia | 78 ( 23) | 46 ( 14) | 17 ( 5) | 51 ( 15) | 26 ( 8) | 7 ( 2) |
| **Gastrointestinal Disorders** | | | | | | |
| Nausea | 134 ( 39) | 10 ( 3) | 0 | 70 ( 21) | 1 ( <1) | 0 |
| Diarrhoea | 119 ( 35) | 19 ( 6) | 2 ( 1) | 20 ( 6) | 1 ( <1) | 0 |
| Vomiting | 87 ( 26) | 13 ( 4) | 0 | 41 ( 12) | 2 ( 1) | 0 |
| Constipation | 77 ( 23) | 2 ( 1) | 0 | 14 ( 4) | 0 | 0 |
| Abdominal Pain Upper | 34 ( 10) | 1 ( <1) | 0 | 20 ( 6) | 0 | 0 |
| **Nervous System Disorders** | | | | | | |
| Peripheral Neuropathy | 156 ( 46) | 42 ( 12) | 2 ( 1) | 4 ( 1) | 0 | 0 |
| Neuralgia | 117 ( 34) | 27 ( 8) | 2 ( 1) | 1 ( <1) | 0 | 0 |
| Paraesthesia | 42 ( 12) | 6 ( 2) | 0 | 4 ( 1) | 0 | 0 |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | 85 ( 25) | 19 ( 6) | 2 ( 1) | 48 ( 14) | 4 ( 1) | 0 |
| Asthenia | 54 ( 16) | 18 ( 5) | 0 | 23 ( 7) | 3 ( 1) | 0 |
| Pyrexia | 53 ( 16) | 4 ( 1) | 0 | 19 ( 6) | 1 ( <1) | 1 ( <1) |
| **Infections and Infestations** | | | | | | |
| Herpes Zoster | 39 ( 11) | 11 ( 3) | 0 | 9 ( 3) | 4 ( 1) | 0 |

| | ---------- 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 |
| **Metabolism and Nutrition Disorders** Anorexia | 64 ( 19) | 6 ( 2) | 0 | 19 ( 6) | 0 | 0 |
| **Skin and Subcutaneous Tissue Disorders** Rash | 38 ( 11) | 2 ( 1) | 0 | 7 ( 2) | 0 | 0 |
| **Psychiatric Disorders** Insomnia | 35 ( 10) | 1 ( <1) | 0 | 21 ( 6) | 0 | 0 |

*Herpes zoster virus reactivation*

Physicians should consider using antiviral prophylaxis in patients being treated with VELCADE. In the VISTA study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with VcMP compared with MP (14% vs 4% respectively). Antiviral prophylaxis was administrated to 26% of the patients in the VcMP arm. The incidence of herpes zoster among patients in the VcMP treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis. Similar results were observed during the IFM2005 study; herpes zoster was more common in patients treated with VELCADE-based regimen compared to control regimen (9.2% vs. 2.1%). During consolidation, the GIMEMA study reported similar rates (0.6%) of grade 3-4 incidences of herpes zoster between the two study arms (*p*=1.0000).

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

The adverse events most commonly reported, regardless of causality, in the APEX study in relapsed / refractory multiple myeloma patients (see **CLINICAL TRIALS**) are presented in Tables 13. All adverse events occurring at ≥10% are included.

**Table 13: Most Commonly Reported (≥10% in VELCADE arm) Adverse Events in the APEX Study using the 1.3 mg/m$^2$ dose (N=663)**

| | VELCADE (N=331) | | | Dexamethasone (N=332) | | |
|---|---|---|---|---|---|---|
| | All Events % | Grade 3 % | Grade 4 % | All Events % | Grade 3 % | Grade 4 % |
| **Adverse Event** | **100** | **61** | **14** | **98** | **44** | **16** |
| **Body as a Whole-General Disorders** | | | | | | |
| Asthenic conditions (fatigue, malaise, weakness) | 61 | 12 | <1 | 45 | 6 | 0 |
| Pyrexia | 35 | 2 | 0 | 16 | 1 | <1 |
| Rigors | 11 | 0 | 0 | 2 | 0 | 0 |
| Oedema lower limb | 11 | 0 | 0 | 13 | <1 | 0 |
| **Gastro-Intestinal System Disorders** | | | | | | |
| 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 and lymphatic system disorders** | | | | | | |
| Thrombocytopenia | 35 | 26 | 4 | 11 | 5 | 1 |
| Anemia | 26 | 9 | <1 | 22 | 10 | <1 |
| Neutropenia | 19 | 12 | 2 | 2 | 1 | 0 |
| **Psychiatric disorders** | | | | | | |
| General | 35 | 3 | <1 | 49 | 5 | 1 |
| Insomnia | 18 | <1 | 0 | 27 | 2 | 0 |
| **Metabolic and Nutritional Disorders** | | | | | | |
| Appetite decreased and anorexia | 34 | 3 | 0 | 9 | <1 | 0 |
| **Respiratory System disorders** | | | | | | |
| Cough | 21 | <1 | 0 | 11 | <1 | 0 |
| Dyspnoea | 20 | 5 | <1 | 17 | 3 | <1 |
| **Skin and subcutaneous tissue disorders** | | | | | | |
| Rash | 18 | 1 | 0 | 6 | 0 | 0 |
| **Infections and infestations** | | | | | | |
| Lower respiratory/lung infections | 15 | 4 | <1 | 21 | 5 | <1 |
| Nasopharyngitis | 14 | <1 | 0 | 7 | 0 | 0 |
| Herpes zoster | 13 | 2 | 0 | 5 | 1 | <1 |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Bone pain | 16 | 4 | 0 | 15 | 3 | 0 |
| Pain in limb | 15 | 2 | 0 | 7 | <1 | 0 |
| Back pain | 14 | 3 | 0 | 10 | 1 | 0 |
| Arthralgia | 14 | <1 | 0 | 11 | 2 | 0 |
| Muscle cramps | 12 | 0 | 0 | 15 | <1 | 0 |
| Myalgia | 12 | <1 | 0 | 5 | <1 | 0 |

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

## Serious Adverse Events (SAEs)

In the APEX study, 44% of patients from the VELCADE treatment arm experienced a SAE during the study, as did 43% of dexamethasone-treated patients. The most commonly reported SAEs in the VELCADE 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 VELCADE and dexamethasone patients respectively were discontinued from treatment due to adverse events assessed as drug related by the investigators. The most common for VELCADE 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 VELCADE-related: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four (4) deaths were considered dexamethasone–related: 2 cases of sepsis, 1 case of bacterial meningitis and 1 case of sudden death at home. In the phase II studies 2 deaths were reported and considered by the investigator to be possibly related to VELCADE: 1 case of cardiopulmonary arrest and 1 case of respiratory failure.

## Adverse reactions

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

**Neoplasms benign, malignant and unspecified (including cysts and polyps)**

Uncommon: tumour lysis syndrome (see **PRECAUTIONS**)

**Blood and lymphatic system disorders**

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

Common: leukopenia, lymphopenia.

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

**Immune system disorders**

Uncommon: hypersensitivity, immunocomplex mediated hypersensitivity.

**Metabolism and nutrition disorders**

Very Common: appetite decreased.

Common: dehydration, hyperglycaemia, hypokalaemia.

Uncommon: hypercalcaemia, hyperkalaemia, hyperuricaemia, hyponatraemia, hypernatraemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia, hypoglycaemia, appetite increased, cachexia, vitamin B12 deficiency.

**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 **PRECAUTIONS**), 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 **PRECAUTIONS**), eye pain.

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

**Ear and labyrinth disorders**

Common: vertigo.

Uncommon: tinnitus, deafness, hypoacusis, hearing impaired.

**Cardiac disorders**

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

Rare: New onset of decreased left ventricular ejection fraction.

**Vascular disorders**

Common: hypotension, orthostatic and postural hypotension (see **PRECAUTIONS**), 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 **PRECAUTIONS**)

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 **PRECAUTIONS**)

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 **PRECAUTIONS**), pyrexia.

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

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

**Investigations**

Common: weight decreased, blood lactate dehydrogenase increased.

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

**Injury, poisoning and procedural complications**

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

**Reproductive system and breast disorders**

Uncommon: testicular pain, erectile dysfunction.

**Potentially immunocomplex-mediated reactions** (see **PRECAUTIONS**)

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

## Post Marketing Experience

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

**Blood and lymphatic system disorders**

Rare: disseminated intravascular coagulation.

**Cardiac Disorders**

Rare: atrioventricular block complete, cardiac tamponade, pericarditis, ventricular arrhythmias, sinus and ventricular tachycardia.

**Ear and labyrinth disorders**

Rare: deafness bilateral.

**Eyes Disorder**

Rare: ophthalmic herpes, optic neuropathy, blindness.

**Gastrointestinal disorders**

Rare: ischemic colitis, acute pancreatitis.

**Hepatobiliary disorders**

Rare: liver failure

**Infections and infestations**

Rare: herpes meningoencephalitis, septic shock

**Immune System Disorders**

Rare: angioedema

**Nervous system disorders**

Rare: encephalopathy, autonomic neuropathy.

**Respiratory, thoracic and mediastinal disorders**

Rare: acute diffuse infiltrative pulmonary disease (see **PRECAUTIONS**), pulmonary hypertension

**Skin and subcutaneous tissue disorders**

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

Very Rare: Stevens-Johnson Syndrome and toxic epidermal necrolysis

# DOSAGE AND ADMINISTRATION

## Recommended Dosage
## Previously Untreated Multiple Myeloma

### *Transplant Eligible*

**1. VELCADE plus thalidomide-dexamethasone**

During the induction stage, VELCADE (bortezomib) is administered twice weekly in combination with thalidomide-dexamethasone for three 3-week treatment cycles. The treatment regimen is shown in Table 14.

**Table 14: Recommended dosage regimen for VELCADE when used in combination with thalidomide and dexamethasone**

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

Vc = VELCADE; t = thalidomide; d = dexamethasone

**2. VELCADE plus dexamethasone**

VELCADE (bortezomib) is administered as an IV injection in combination with oral dexamethasone for four 3-week treatment cycles as shown in Table 15.

**Table 15: Recommended dosage regimen for VELCADE when used in combination with dexamethasone**

| **Week** | **1** | | **2** | | | | **3** |
|---|---|---|---|---|---|---|---|
| Vc (1.3 mg/m$^2$) | Day 1 | Day 4 | Day 8 | -- | Day 11 | -- | -- |
| d (40 mg)-All Cycles | Day 1-4-- | | -- | | | | -- |
| d (40 mg)-Cycle 1-2 | | | Day 9-12 | | | | -- |

Vc = VELCADE; d = dexamethasone

### *Non-Transplant Eligible*

VELCADE (bortezomib) is administered as a 3-5 second bolus IV injection in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 16. In Cycles 1-4, VELCADE is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, VELCADE is administered once weekly (days 1, 8, 22 and 29).

**Table 16: Recommended Dosage Regimen for VELCADE when used in combination with melphalan and prednisone for Patients with Previously Untreated Multiple Myeloma**

| Twice Weekly VELCADE (Cycles 1-4) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **1** | | | | **2** | | **3** | **4** | | **5** | | **6** |
| Vc (1.3 mg/m$^2$) | Day 1 | -- | -- | Day 4 | Day 8 | Day 11 | rest period | Day 22 | Day 25 | Day 29 | Day 32 | rest period |
| m(9 mg/m$^2$) | Day 1 | Day 2 | Day 3 | Day 4 | -- | -- | rest period | -- | -- | -- | -- | rest period |
| p(60 mg/m$^{2)}$ | | | | | | | | | | | | |

| Once Weekly VELCADE (Cycles 5-9) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Week** | **1** | | | | **2** | **3** | **4** | **5** | **6** |
| Vc (1.3 mg/m$^{2)}$ | Day 1 | -- | -- | -- | Day 8 | rest period | Day 22 | Day 29 | rest period |
| m (9 mg/m$^2$)<br>p (60 mg/m$^2$) | Day 1 | Day 2 | Day 3 | Day 4 | -- | rest period | -- | -- | rest period |

Vc = VELCADE; m = melphalan, p=prednisone

## Dose Management Guidelines

Dose modification and re-initiation of therapy when VELCADE is administered in combination with melphalan and prednisone

Prior to initiating a new cycle of therapy:

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

**Table 17: Dose Modifications during Subsequent Cycles:**

| **Toxicity** | **Dose modification or delay** |
|---|---|
| **Haematological toxicity during a cycle:** | |
| • If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle | Consider reduction of the melphalan dose by 25% in the next cycle. |
| • If platelet count ≤30 × $10^9$/L or ANC ≤0.75 x $10^9$/L on a VELCADE dosing day (other than day 1) | Velcade dose should be withheld |
| • If several VELCADE doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration) | VELCADE dose should be reduced by 1 dose level (from 1.3 mg/m$^2$ to 1 mg/m$^2$, or from 1 mg/m$^2$ to 0.7 mg/m$^2$) |
| GRADE ≥ 3 NON-HAEMATOLOGICAL TOXICITIES | VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m$^2$ to 1 mg/m$^2$, or from 1 mg/m$^2$ to 0.7 mg/m$^2$).<br>For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 18. |

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

**Table 18: Recommended Dose Modification for VELCADE-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy.**

| **Severity of Peripheral Neuropathy Signs and Symptoms** | **Modification of Dose and Regimen** |
|---|---|
| Grade 1 (paraesthesias, weakness and/or loss of reflexes) without pain or loss of function | No action |
| Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living) | Reduce VELCADE to 1.0 mg/m$^2$ |
| Grade 2 with pain or Grade 3 (interfering with activities of daily living) | Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m$^2$ and change treatment schedule to once per week. |
| Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis) | Discontinue VELCADE |

NCI Common Toxicity Criteria

## Relapsed / Refractory Multiple Myeloma

The recommended dose of VELCADE is 1.3 mg/m$^2$/dose administered as a 3-5 second bolus intravenous injection 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 VELCADE.

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

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

### Dose Modification and Reinitiation of Therapy

VELCADE therapy should be withheld at the onset of any Grade 3 non-haematological or Grade 4 haematological toxicities excluding neuropathy as discussed above (see **PRECAUTIONS**). Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a 25% reduced dose (1.3 mg/m$^2$/dose reduced to 1.0 mg/m$^2$/dose; 1.0 mg/m$^2$/dose reduced to 0.7 mg/m$^2$/dose). Table 18 above contains the recommended dose modification for the management of patients who experience VELCADE-related neuropathic pain and/or peripheral sensory neuropathy. Patients with pre-existing severe neuropathy should be treated with VELCADE only after careful risk/benefit assessment.

### Patients with Renal Impairment

Based on the data from a small study, the pharmacokinetics of VELCADE are not influenced by mild or moderate renal impairment. Therefore, dosing adjustments of VELCADE are not necessary for these patients. The effect of severe renal impairment (CrCl < 20mL/min/1.73m$^2$) has not been determined. Since dialysis may reduce VELCADE concentrations, the drug should be administered after the dialysis procedure (see **PHARMACOKINETICS)**.

### Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELCADE dose. Patients with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0.7 mg/m$^2$ per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m$^2$ or further dose reduction to 0.5 mg/m$^2$ may be considered based on patient tolerance (see Table 19).

**Table 19: Recommended Starting Dose Modification for VELCADE 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 VELCADE to 0.7 mg/m$^2$ in the first cycle. Consider dose escalation to 1.0 mg/m$^2$ or further dose reduction to 0.5 mg/m$^2$ in subsequent cycles based on patient tolerability. |
| Severe | > 3x ULN | Any | |

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

### Administration

VELCADE is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0.9% sodium chloride solution for injection.

### Instructions for Use and Handling and Disposal

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

*Reconstitution/Preparation for Intravenous Injection:* Prior to use, the contents of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline, Sodium Chloride for Injection. The reconstituted product should be a clear and colourless solution.

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

*Procedure for proper disposal:* Any unused product or waste material should be disposed of in accordance with local requirements.

## OVERDOSAGE

Cardiovascular safety pharmacology studies in monkeys and dogs showed that IV doses approximately two to three times the recommended clinical dose on a mg/m$^2$ basis are associated with increases in heart rate, decreases in contractility, hypotension and death. The decreased cardiac contractility and hypotension responded to acute intervention with positive ionotropic or pressor agents. In dog studies, a slight increase in the corrected QT interval was observed at a lethal dose.
In patients, overdosage more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.

There is no known specific antidote for VELCADE 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 **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).
Refer to Australian Poisons Information Centre for further information (telephone number: 131126).

## PRESENTATION AND STORAGE CONDITIONS

VELCADE is supplied in a 5 mL or 10 mL, type I, glass vial with a gray bromobutyl stopper and aluminum seal. The cap colour of the 5 mL vial is green, and the cap colour for the 10 mL vial is royal blue. The vial is contained in a transparent blister pack consisting of a tray with a lid. The 5 mL vial contains 11 mg powder (1.0 mg bortezomib) for injection and the 10 mL vial contains 38.5 mg powder (3.5 mg bortezomib) for injection. The 5 mL vial (1.0mg bortezomib) is currently not marketed.

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

### Storage

*Unopened vials:* Store below 25ºC. Keep the container in the outer carton in order to protect from light.

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

## NAME AND ADDRESS OF THE SPONSOR

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Rd Macquarie Park NSW 2113 Australia

NZ Office: Auckland New Zealand

®VELCADE is the registered trademark of Millennium Pharmaceuticals for bortezomib injections.

## POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

## DATE OF FIRST INCLUSION IN THE ARTG: 14 February 2006
## DATE OF MOST RECENT AMENDMENT: 31 October 2011

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
**www.tga.gov.au**

Reference/Publication #