SCIENTIFIC DISCUSSION

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel:(44-20) 74 18 84, fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int, http://www.emea.eu.int

1. Introduction

VELCADE for injection was granted accelerated approval by the United States (US) Food and Drug Administration (FDA) on 13 May 2003. On 26 April 2004, VELCADE was approved under exceptional circumstances in the EU with the following indication:

"VELCADE is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy."

The initial approval in the EU was based on response as a surrogate marker for clinical benefit. In order to definitively demonstrate that VELCADE provides clinical benefit to patients, the MAH conducted a large, international, randomized, controlled Phase III study, M34101-039, in a patient population earlier in the course of their disease (1-3 prior therapies). Study 039 directly compared VELCADE to a standard therapy with pulse, high-dose dexamethasone. At the time of the Initial Marketing Authorisation In the EU, the MAH made a commitment to submit the final report of this study with their responses to a Specific Obligation.

Based on the results from study 039, the MAH is hereby applying to extend the current indication as follows:

"VELCADE is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy."

3.2. A proposed addition to the dosage and administration section was also included in the prescribing information. Besides efficacy data the Phase III Study M34 101-039 also provided safety information supporting of the revision to the following sections of the SPC section 4.4 Special warnings and special precautions for use. The MAH also proposes to update SPC section 5.1 Pharmacodynamic properties to include the new clinical data generated by study 039. Finally, the Patient Information Leaflet has been revised according to these changes.

2. Clinical aspects

Clinical Pharmacology

Not applicable.

Clinical Efficacy

The clinical efficacy programme included one pivotal Phase III study (M34101-039), which was a randomised, open-label trial designed to determine whether bortezomib provided superior clinical benefit to patients with relapsed or refractory multiple myeloma compared to high-dose dexamethasone. Efficacy assessments were based on time to progression (TTP), overall and one year survival time and Quality of Life (QOL). Safety was assessed by the occurrence of clinical and laboratory toxicities and changes from baseline in physical examination findings, vital signs, and if applicable, chest X-ray and electrocardiogram findings.

The main study was supported by 3 phase II efficacy studies (M34101-024, M34101-025, M34101-029) and one phase IIb efficacy study (M34101-040 ongoing).

A series of phase 1 studies were designed to determine the appropriate dose and schedule for phase 2 studies and to define the toxicity profile of bortezomib. These studies provided the data to support the selection of the twice-weekly schedule at 1.3 mg/m^2 as the most appropriate dose for further evaluation of bortezomib in patients with multiple myeloma.

Pivotal study

Study M34101-039: An International, Multi-Center, Randomized, Open-Label Study of PS-341 Versus High-Dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

GCP

The Applicant states that the clinical Study M34101-039 was designed and performed in accordance with good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines. Data have been subjected to monitoring and 100% source documentation. Internal sponsor audits have been performed at 21 of the 93 study sites, including 11 of the 12 highest enrolling sites (5 US and 6 ex-US), and confirm the integrity of the data collected.

Objectives

The primary objective was to determine whether bortezomib provided superior benefit to patients with relapsed or refractory multiple myeloma compared to high-dose dexamethasone, as assessed by significant prolongation of time to progression (TTP) and supported by improvement in selected measures of clinical benefit and also to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone.

Secondary efficacy objectives were to determine whether treatment with bortezomib prolonged survival time (overall and one year) relative to treatment with high-dose dexamethasone, to assess the potential superiority of bortezomib to high-dose dexamethasone, as determined by the rates of CR and PR to treatment. Overall survival was defined as the duration from the date of randomization to the date of death. One-year survival, defined as deaths occurring within one year of randomization, also was to be evaluated.

An exploratory efficacy objective was to determine whether treatment with bortezomib was associated with a better quality of life (QOL) relative to treatment with high-dose dexamethasone.

The safety objective was to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, as determined by the incidence of clinical and laboratory toxicities.

Study population

A total of 669 patients at 93 centres were enrolled between May 2002 and October 2003.

Patients were enrolled at 93 international study centers, in Canada, the EU and Israel. Elegible for the study were patients previously diagnosed with multiple myeloma based on standard criteria; requiring second-, third- or fourth-line therapy because of progressive disease (defined as at least a 25% increase in M-protein, or development of new or worsening of existing lytic bone lesions or soft tissue plasmacytomas, or hypercalcemia [serum calcium >11.5 mg/dL], or relapse from complete response at any time after or during their last therapy. Unlike Study M34100-025, patients enrolled in Study M34101-039 were not required to be refractory to their last therapy.
Eligible patients were required to have Karnofsky performance status score $\geq$60%, platelet count $\geq$50 × 109/L and hemoglobin $\geq$.5 g/dL without transfusion support within the 7 days before the test; absolute neutrophil count (ANC) $\geq$.75 × 109/L without the use of growth factors; and calculated or measured creatinine clearance e20 mL/minute. Patients who were refractory to high-dose dexamethasone were excluded from the study, since these patients would be expected either not to respond to dexamethasone or have a short response duration. A specific definition was provided in the protocol to clearly define this patient population.

The number of protocol violations is high: 140 of 669 patients (21%). The inclusion of a substantial proportion of dexamethasone-refractory patients (28/336 patients, 8%) is particularly disappointing.

Summary of Inclusion and Exclusion Criteria Violations as Reported by the Investigator (ITT Population, N = 669)

Inclusion/Exclusion Criteria Violation	VELCADE n (%) (n = 333)	Dexamethasone n (%) (n = 336)	Total n (%) (n = 669)
Refractory to dexamethasone [a]	32 (10)	28 (8)	60 (9)
Laboratory criteria violation	10 (3)	10 (3)	20 (3)
Received immunotherapy within 8 wks, nitrosoureas within 6 wks, or other chemotherapy, corticosteroids (>10 mg/day prednisone equivalent) or radiation therapy within 3 wks	8 (2)	10 (3)	18 (3)
Non-measurable disease – oligo- or non-secretory myeloma	10 (3)	7 (2)	17 (3)
Diagnosed with myeloma requiring 2nd, 3rd, or 4thline therapy because of PD	4 (1)	10 (3)	14 (2)
Treated for other cancer within 5 years	1 (<1)	2 (<1)	3 (<1)
Non-measurable disease – secretory myeloma	1 (<1)	1 (<1)	2 (<1)
Previously treated with VELCADE	1 (<1)	1 (<1)	2 (<1)
Informed consent violation	0	1 (<1)	1 (<1)
Karnofsky performance status <60%	0	1 (<1)	1 (<1)
Cardiac amyloidosis	1 (<1)	0	1 (<1)
Serious medical condition	0	1 (<1)	1 (<1)

a Based on a sponsor-derived computer algorithm; all other reported violations are derived from the Inclusion and Exclusion CRF.

Treatments

Bortezomib:
Patients assigned to the bortezomib group were to receive treatment for a maximum of 273 days. Patients in this treatment group were to receive up to eight 3-week treatment cycles followed by up to three 5-week treatment cycles of bortezomib. Within each 3-week treatment cycle, the patient was to receive bortezomib 1.3 mg/m^2/dose alone as a bolus intravenous (IV) injection twice weekly for two weeks (on Days 1, 4, 8, and 11) of a 21-day cycle. Within each 5-week treatment cycle, the patient was to receive bortezomib 1.3 mg/m^2/dose alone as a bolus IV injection once weekly (on Days 1, 8, 15, and 22) of a 35-day cycle.
During the discussion, the CHMP asked the MAH to provide justification for the 8 treatment cycles and to further assess the optimal number of cycles. The MAH has committed to investigate this point.

Dexamethasone:
Patients assigned to the high-dose dexamethasone group were to receive treatment for a maximum of 280 days.
Patients assigned to the high-dose dexamethasone group were to receive up to four 5-week treatment cycles followed by up to five 4-week treatment cycles. Within each 5-week treatment cycle, the patient was to receive dexamethasone 40 mg/day PO, once daily on Days 1 to 4, 9 to 12, and 17 to 20 of a 35-day cycle. Within each 4-week treatment cycle, the patient was to receive dexamethasone 40 mg/day PO once daily on Days 1 to 4 of a 28-day cycle. The protocol provided for all patients in the dexamethasone group who experienced confirmed disease progression to cross over and receive VELCADE on the companion study M34101-040.

This decision to use high-dose dexamethasone as the control treatment was taken considering that 1) although there was no single standard therapy for patients who had been previously treated for multiple myeloma, pulse high-dose dexamethasone was one of the most widely accepted options; 2) high-dose dexamethasone had been specifically developed as a second-line therapy for patients who had previously been treated with regimens based on alkylating agents and corticosteroids; 3) a broad range of patients were eligible for treatment with high-dose dexamethasone, including older patients and those who had compromised bone marrow function as a result of ASCT or prolonged alkylator

therapy; 4) at least 4 other ongoing phase 3 trials (in the US and EU) were being conducted by other sponsors in patients with multiple myeloma using dexamethasone as the control arm.

Outcomes/endpoints

The primary endpoint of the study M34101-039 was time to progression (TTP), defined as the duration from the date of randomization until the date of first documented evidence of progressive disease (PD) (or relapse for patients who experienced CR. The date of PD was determined as the date of the first indication of progression (e.g., sufficient elevation of M-protein, new skeletal event).

Secondary endpoints were improvement in selected measures of clinical benefit, such as overall survival, one-year survival, overall response rate, duration of response, time to first evidence of confirmed response, incidence of Grade 3 or worse infection, development of skeletal events, and other patient-reported-outcomes, such as symptom scores and quality of life surveys.

Disease response and progression were assessed during the phase III study according to the European Group for Blood and Marrow Transplant (EBMT) criteria. The specific efficacy parameters included central laboratory analysis of serum protein by electrophoresis, urine protein by electrophoresis, and serum corrected calcium levels, local site evaluation of skeletal surveys, plasmacytomas, and bone marrow plasma cell content, reflect the disease and its pathogenesis.
Assessment of disease response using non-invasive procedures was to be performed every 3 weeks during treatment; at the End of Treatment visit (Week 42), which was to be a minimum of 30 days following the final dose; and during Short-Term Follow-Up.

Safety was assessed by the occurrence of clinical and laboratory toxicities and changes from baseline in physical examination findings, vital signs, and if applicable, chest X-ray and electrocardiogram findings. A neurotoxicity-directed questionnaire from the Functional Assessment of Cancer/Gynecology Oncology Group (FACT/GOG) was also administered to evaluate the onset and intensity of peripheral neuropathy and other neurotoxicities.

Criteria for the determination of PD or Relapse:

Progressive disease (PD) (for patients not in CR)	Requires one or more of the following: • >25% increase in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed on a repeat investigation 1 to 3 weeks later.[d, e] • >25% increase in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed on a repeat investigation 1 to 3 weeks later[d,e]. • >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%. • Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas. • Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture). • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause)[d].
Relapse from CR	Requires at least one of the following: • Reappearance of serum or urine monoclonal paraprotein on immunofixation or routine electrophoresis to an absolute value of ≥5 g/L for serum and ≥200 mg/24 hours for urine, and excluding oligoclonal immune reconstitution. Reappearance of monoclonal paraprotein must be confirmed by at least one follow-up 6 weeks later. • ≥5% plasma cells in the bone marrow aspirate or biopsy. • Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (not including compression fracture). • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause).

Randomisation

Patients who were determined to be eligible for the study were to be assigned to 1 of the 2 dose groups (bortezomib 1.3 mg/m^2/dose or high-dose dexamethasone) at a 1:1 ratio by random allocation. Randomization to each dose group was stratified, based on the amount of prior lines of therapy the patient had received (1 prior line of therapy versus more than 1 prior line of therapy), whether the patient experienced progressive disease while on their most recent therapy or within 6 months of stopping their most recent therapy, or if the patient relapsed >6 months after receiving their most recent treatment regimen, and screening ß2-microglobulin levels (>2.5 mg/L versus ≤2.5 mg/L),

Blinding

The study was open-label in design, as the nature of the treatments under evaluation (with expected different adverse event profiles) and the different administrations (IV versus oral) made it not possible the implementation of effective blinding procedures.

Several steps were taken to reduce potential biases associated with the choice of the endpoint (TTP), the comparator used (dexamethasone), the open-label design and to eliminate/minimize any potential bias in the analysis of laboratory, such as: 1) serum and urine M-protein, clinical chemistry and hematology tests were analyzed at a central laboratory in order to reduce the variance in laboratory data, particularly regarding interpretation of immunofixation and quantification of M-protein, which include qualitative interpretation; 2) since diagnosis of confirmed Progressive disease during the treatment period resulted in discontinuation of study drug, it was important that determination of Progressive disease was according to the European Group for Blood and Marrow Transplant (EBMT) criteria, and that these criteria were applied consistently to both treatment groups, and among all sites, therefore investigators were required to fax information that included all data supporting the diagnosis of Progressive disease for review by at least one of the study medical monitors; 3) determination of both Progressive disease and best response were based on a computer algorithm that had been validated by IRC review of efficacy data from a subset of patients; 4) patients who where refractory to high-dose dexamethasone were excluded from the study, since these patients would be expected either

not to respond to dexamethasone or have a short response duration; 5) since the primary endpoint of the study was TTP, the treatment regimens were designed such that the total length of treatment was similar in both groups (273 days on VELCADE and 280 days on dexamethasone), and the interval between disease assessments (including serum and urine immunofixation and M-protein quantification) was short (3 weeks) and identical in both treatment groups .

Statistical methods

The sample size of 620 patients was based on the requirement for 462 PD events in order to provide 80% power to detect a significant difference in TTP with alpha=0.05. This assumed an estimated median TTP of 8 months for dexamethasone and 10.4 months for VELCADE (ratio of median TTP of 1.30 for VELCADE relative to high-dose dexamethasone) and a patient accrual period of 9 months, with a planned analysis 14 months after the last patient accrued. The estimate for the expected TTP was based on the results of small phase 2 studies. It was recognized that the TTP estimate for dexamethasone used for the sample size determination was likely longer than would be observed in a large, international, randomized study.

The final analyses of primary and secondary efficacy endpoints were performed on the ITT population. Analyses of disease response, time to response and duration of response were performed on the Response Population, defined as patients who received at least one dose of study treatment and who had measurable disease at baseline.

TTP was defined as the time from the date of randomization to the date of first evidence of disease progression or to relapse for patients who experienced complete response; the date of progression was determined using a computer algorithm based on the EBMT criteria. Censoring of data was conducted for patients who started alternate chemotherapy, were lost to follow-up, or died before documentation of PD.

Survival was defined as the time from the date of randomization to the date of death. Censoring of data was conducted for patients who were alive at last follow-up up through 13 January 2004; data for patients who were randomized but not treated were censored at the date of randomization. At the time of this analysis, median duration of follow-up for surviving patients was 8.3 months.

The primary efficacy analysis was the stratified log-rank test for the comparison of TTP between the VELCADE and dexamethasone treatment groups (two-sided, alpha=0.05 level of significance). Treatment group differences for each of the secondary endpoints were also tested at the two-sided, alpha=0.05 level of significance. Analyses of efficacy results were performed for patient subgroups based on randomized stratification and on age and sex.

When appropriate, descriptive and statistical results are presented for “All patients” and for the subgroup “with 1 prior line of therapy” in order to verify the effectiveness of VELCADE in the specific subgroup of patients receiving the drug as second-line therapy. In addition, sensitivity analyses were carried out in patients who were reported by the investigators to be “Refractory to their last therapy” or “Refractory to dexamethasone“ according to a sponsor-derived computer algorithm.

The study design for M34101-039 included a single prospectively-defined interim analysis for TTP to be performed when half of the total required number of progressive disease events had occurred (a total of 231 patients having PD). Statistical significance was to be declared at the interim analysis if the logrank p-value was $\leq$0.005, and, failing this, at the final analysis if the p-value was $\leq$0.048. The protocol design also included an independent Data Monitoring Committee (DMC) to evaluate safety data and results of the prospectively-defined interim analysis of efficacy.

Two DMC meetings were held during the conduct of this study. At the time of second meeting on 3 December 2003, a total of 669 patients had been enrolled and a total of 254 PD events were included. A total of 657 patients were included in the ITT population. The results of the interim analysis revealed a highly significant difference between treatment groups with regard to TTP, with a longer median TTP in the VELCADE group compared to the dexamethasone group ($p<0.0001$). Overall

survival also was prolonged in the VELCADE group compared to the dexamethasone group (p=0.038)**.** According to the results, the DMC recommended that the control arm be halted and that all patients randomized to dexamethasone be given the opportunity to receive treatment with VELCADE as soon as possible. Based on the DMC recommendations and after discussion or notification to the Regulatory Agencies, the Sponsor permitted all patients assigned to dexamethasone to discontinue treatment and receive VELCADE, whether or not they had experienced disease progression and regardless of the time since discontinuation from Study M34101-039 or interval treatment with alternate therapies between studies. During the discussion, the MAH committed to provide data on patients that as a result of the DMC decision on study 039 were permitted to receive treatment with VELCADE regardless their prior randomised allocation and were followed up in study 040. Because of the decision to allow cross over from dexamethasone to VELCADE in the absence of progressive disease, legitimate statistical comparisons between the VELCADE and dexamethasone groups, including comparisons of survival, are not possible after 13 January 2004 as, after that date, patients were provided the option to cross over from dexamethasone to VELCADE. As important consequence of this decision, the follow-up period for comparative analyses of survival is limited, and all final efficacy analyses were censored at the last efficacy observation on or before 14 December 2003.

RESULTS

A total of 669 patients with multiple myeloma were randomized in this study at 93 study centers in North America, Europe and Israel; 333 (50%) of the 669 patients were randomized to receive bortezomib and 336 (50%) were randomized to receive dexamethasone. These 669 patients comprise the ITT population for analyses of baseline and efficacy data. A total of 253 (38%) of the 669 patients were randomized at study centers in the US, 416 (62%) in Canada, the European Union and Israel. A total of 6 patients who were randomized did not receive study drug, including 2 patients randomized to bortezomib and 4 to dexamethasone.

A total of 663 patients received at least one dose of study drug, including 331 treated with bortezomib and 332 treated with dexamethasone. These 663 patients comprise the safety population.

Demography at baseline

Demographic and baseline disease characteristics across the treatment groups are shown in the table below. Demographic and baseline disease characteristics were balanced across the treatment groups. The two treatment groups were comparable with regard to the number and types of prior therapies administered: the median number of prior therapeutic lines administered was 2 in both groups (range of 1 to 8). The two treatment groups were also comparable with regard to the types of last therapy administered, the duration of the last prior therapy and the mean time from last prior therapy to study treatment, for the subgroup of patients who received only one prior line of therapy and for the subgroup who had received more than one prior line. Treatment groups were all balanced in terms of the kind of last therapy prior the study entry.

Table 2.5.4-1 Demographic and Baseline Disease Characteristics (Study M34101-039, ITT Population)

Characteristic	VELCADE			Dexamethasone		
	1 Prior Line (N=132)	>1 Prior Line (N=200)	Total (N=333)	1 Prior Line (N=119)	>1 Prior Line (N=217)	Total (N=336)
Age, median (years)	62	62	62	62	61	61
% Male	54	59	56	55	62	60
% Caucasian	89	91	90	88	87	88
% KPS ≥80	94	82	87	84	83	83
Type of Myeloma:						
%IgG	67	56	60	62	58	59
% IgA	19	26	23	22	24	24
% Light chain	12	13	12	12	14	13
Duration since diagnosis, median (years)	2.3	4.1	3.5	2.3	3.7	3.1
Median β_2-microglobulin (mg/L)	3.3	4.0	3.7	3.1	4.1	3.6
% Hemoglobin <100 g/L	25	37	32	24	31	28
% Platelet count $<75\times10^9$/L	6	7	6	4	5	4

Source: Module 5, M34101-039, section 14.1, Table 14.1.2, Table 14.1.2.1, Table 14.1.3.1, Table 14.1.3.1A, Table 14.1.3.3 and Table 14.1.3.3A.

Note: One patient in the VELCADE group was missing prior therapy data.

The majority of patients in both treatment groups had received 1 to 3 prior lines of therapy, including 318 (96%) of 332 VELCADE patients with data available and 313 (93%) of 336 dexamethasone patients.

Among all 669 patients in the ITT population, a total of 657 (98%) of 668 patients had received prior treatment with steroids (e.g., prednisone in the MP combination, dexamethasone alone or in the VAD combination), and 612 (91%) and 513 (77%) patients, respectively, had received prior alkylating agent therapy (e.g., melphalan alone or in combination with prednisone) or anthracyclines (e.g., Adriamycin as part of the VAD regimen, or mitoxantrone). The proportion of patients who received steroids (VELCADE, 98%; dexamethasone, 99%), alkylating agents (VELCADE, 91%; dexamethasone, 92%), and anthracyclines (VELCADE, 77%; dexamethasone, 76%) was similar in each treatment group.

Although not approved for the treatment of multiple myeloma, 328 (49%) of the 668 patients, 160 (48%) of 332 patients in the VELCADE group and 168 (50%) of 336 patients in the dexamethasone group, had received prior therapy with thalidomide.

A total of 269 (40%) of the 668 patients, including 124 (37%) of 333 patients in the VELCADE group and 145 (43%) of 336 patients in the dexamethasone group had received prior treatment with high-dose dexamethasone.

Prior stem cell transplant or other high-dose therapy had been administered in a total of 451 (68%) of 668 patients, 222 (67%) of 332 patients in the VELCADE group and 229 (68%) of 336 patients in the dexamethasone group.

A total of 60 (9%) of the 669 patients were determined by computer algorithm to be refractory to dexamethasone (not eligible, according to the protocol entry criteria), including 32 (10%) of 333 VELCADE patients and 28 (8%) of 336 dexamethasone patients.

A total of 251 patients (38%) had received only one prior line of therapy, including 40% of patients in the VELCADE group and 35% of patients in the dexamethasone group. Among those 251 patients, most had received generally accepted effective therapy: 85% had received an alkylating agent and 71% had received an anthracycline: the use of thalidomide was lower in both treatment groups (19% and 24% in the VELCADE and dexamethasone groups, respectively) for those patients who had received only one prior line of therapy compared to those who had received more than one prior line (68% and 65% in the VELCADE and dexamethasone groups, respectively).

As to the last therapy prior the study entry, chemotherapy with alkylating agents or other combination chemotherapy was the last prior therapy in 235 (71%) of the 333 VELCADE patients and in 230 (68%) of the 336 dexamethasone patients. Thalidomide alone or in combination was the last therapy

administered prior to study entry in 40% of patients in both treatment groups. The median duration of last prior therapy was 7.0 months in the VELCADE treatment group and 7.1 months in the dexamethasone treatment group and the median time from last dose of chemotherapy to the initiation of study treatment was 5.0 months in the VELCADE group and 4.8 months in the dexamethasone group.

Table 2.7.3-5 Previous Therapy for Multiple Myeloma, Overall and by Treatment Group (Study M34101-039, ITT Population; N=669)

	All Patients		Pts with 1 Prior Line of Therapy	
Therapy	**VELCADE N (%) (n = 333)**	**Dexamethasone N (%) (n = 336)**	**VELCADE N (%) (n = 132)**	**Dexamethasone N (%) (n = 119)**
Median No. of prior therapeutic lines	2.0	2.0	1.0	1.0
1 prior line	132 (40)	119 (35)	132 (100)	119 (100)
2 to 3 prior lines	186 (56)	194 (58)	0	0
4 or more prior lines	14 (4)	23 (7)	0	0
Missing[a]	1	0	0	0
Types of Prior Therapies, N	332	336	132	119
Prior steroids	325 (98)	332 (99)	125 (95)	117 (98)
Prior high-dose dexamethasone	124 (37)	145 (43)	48 (36)	54 (45)
Prior alkylating agents	302 (91)	310 (92)	114 (86)	99 (83)
Prior anthracyclines	256 (77)	257 (76)	96 (73)	81 (68)
Prior thalidomide therapy	160 (48)	168 (50)	25 (19)	28 (24)
Received at least 2 of the above[b]	326 (98)	331 (99)	126 (95)	115 (97)
Received at least 3 of the above[b]	272 (82)	281 (84)	90 (68)	79 (66)
Received all 4 of the above[b]	114 (34)	119 (35)	13 (10)	12 (10)
Received alkylator or anthracycline	328 (98)	327 (97)	129 (98)	110 (92)
Revlimid/Actimid	0	2 (<1)	0	0
Prior Vinca alkaloids	248 (74)	242 (72)	94 (71)	77 (65)
Prior SCT/other high-dose therapy	222 (67)	229 (68)	84 (64)	72 (61)
Prior experimental /other therapy	11 (3)	8 (2)	2 (2)	3 (3)

Source: Module 5, M34101-039, section 14.1, Table 14.1.4.1, Table 14.1.4.1A and Table 14.2.1.3.
a Patient No.158-002, patient was randomized but not treated, no data available.
b Received 2, 3 or 4 of the following: steroids, alkylating agents, anthracyclines, or thalidomide.

A total of 648 (97%) of the 669 patients, including 324 (97%) of 333 patients in the VELCADE group and 324 (96%) of 336 patients in the dexamethasone group, had evidence of progressive disease prior to study entry based on review of CRF data. Progressive disease was most commonly evidenced by a >25% increase in M-protein, either in serum or urine. Only in 17% of patients, including 21% and 13% of patients in the VELCADE and dexamethasone treatment groups, respectively, new lytic bone lesions, or an increase in the size of existing lesions were reported as evidence of progressive disease

It has to be considered that at the time of final analysis, 29% of patients in the bortezomib arm had completed all 8 cycles of induction therapy, and 9% had completed a full course of therapy (11 cycles). The average number of bortezomib doses across the entire study was 22.4, with a range of 1 to 44. In the dexamethasone arm, 36% of patients had completed all 4 cycles of induction therapy, and 5% had completed a full course of therapy (9 cycles). The number of patients, who had completed all 8 cycles or a full course of therapy, was quite low.

Primary endpoint:

Time to progression (TTP)

Overall, 343 patients progressed, 147 in the VELCADE group and 196 in the dexamethasone group. Time to disease progression (TTP) is analysed for all 669 patients included in the ITT population and for those 251 patients who had received only one prior line of therapy. In all ITT patients, median TTP was 189 days (hazard ratio=0.55; 95% CI:0.44-0.69, p=0.0001). In 251 patients who had received only one prior line of therapy, median TTP was 212 days (7.0 months) on VELCADE and 169 days (5.6 months) on dexamethasone (hazard ratio=0.56; 95% CI:0.38-0.81, p=0.0021).

Efficacy Results (ITT Population)

Endpoint	VELCADE N=333	Dexamethasone N=336	Hazard Ratio; p-value
Median TTP, days (months)	189 (6.2)	106 (3.5)	0.55; <0.0001[a]
Median Overall Survival, days (months)	504 (16.6)[b]	NE	0.57; 0.0013[a]
Likelihood of 1-year survival, %	80	66	0.0025[c]
Overall response rate (CR+PR), %[e]	38	18	<0.0001[d]
Median time to response, days[e]	43	43	ND
Median duration of response, days (months)[e]	242 (8.0)	169 (5.6)	ND

NE = not estimable; ND = not done

Note 1: Data for analysis of TTP and response censored on or before 14 December 2003 and for survival, on or before 13 January 2004; date of progression determined by computer algorithm.

Note 2: Hazard ratio <1 favors VELCADE (i.e., lower hazard rate for VELCADE).

a p-value from log-rank test adjusted by randomization stratification factors.

b Median based on the death of one patient; at that time, the curve had accounted for 330 of the 333 patients (with 50 deaths and 280 patients censored) with only one patient death and 2 censored data points after the drop below 50%. The median is likely to change after follow-up data are received for VELCADE patients.

c p-valued from comparison of survival probabilities at one year based on normal approximation.

d p-value from Cochran-Mantel-Haenszel chi-square test adjusted by randomization stratification factors.

e Analyses conducted on the response population: VELCADE: N=315; dexamethasone: N=312

The majority of the 343 patients who had progressed were determined to have disease progression based on central laboratory assessments. Site performed tests, including skeletal surveys for bone lesions, bone marrow evaluations or radiological imaging and physical examination for plasmacytomas, were used as the primary determination of Progressive disease in 60 (17%) of the 343 patients, including 23 (16%) of the 147 VELCADE patients and 37 (19%) of the 196 dexamethasone patients.

Summary of Computer-Algorithm Determined Reasons for PD (Population: Patients with PD)

Primary Reason for Determination of PD	VELCADE n (%) (n = 147)	Dexamethasone n (%) (n = 196)
Central Laboratory Analyses:	124 (84)	159 (81)
Serum M-protein results[a]	71 (48)	98 (50)
Urine M-protein results[b]	44 (30)	60 (31)
Hypercalcemia	9 (6)	1 (<1)
Site Performed Analyses:	23 (16)	37 (19)
Plasmacytoma	14 (10)	15 (8)
Bone lesion	5 (3)	18 (9)
Bone marrow	4 (3)	3 (2)
Bone lesion and bone marrow	0	1 (<1)

a Serum M-protein with or without bone lesion, bone marrow or urine M-protein.

b Urine M-protein with or without bone lesion, bone marrow, plasmacytoma or hypercalcemia.

A total of 60 (9%) of the 669 patients randomized into the study were determined by a sponsorderived computer algorithm to be refractory to dexamethasone, including 32 (10%) of 333 bortezomib patients and 28 (8%) of 336 dexamethasone patients. As these patients would be expected not to respond to dexamethasone, or to have a more short-lived response, a sensitivity analysis was conducted excluding these patients from the analysis. Endpoints analyzed included TTP, survival, and response.

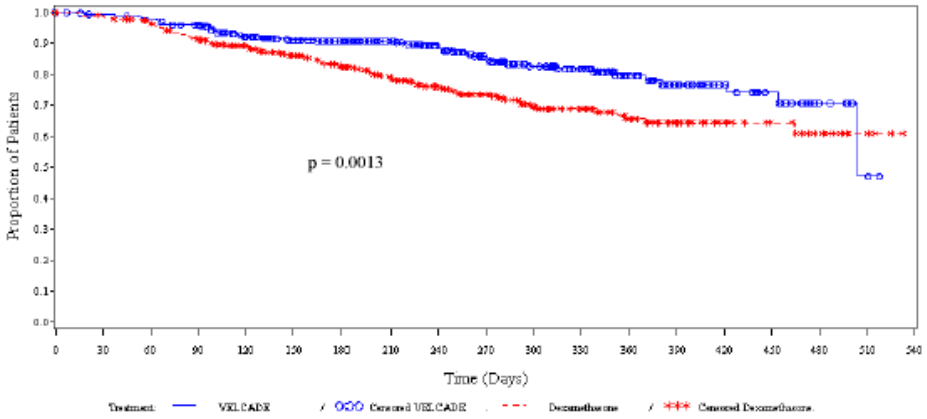
Among those 28 patients determined to be refractory to dexamethasone who received this treatment during study, TTP was similar at 106 days to those 308 dexamethasone patients determined not to be refractory to dexamethasone.

Secondary Endpoints:

Overall and 1-year survival

Overall, 135 patients died, 51 in the VELCADE group and 84 in the dexamethasone group. Overall and one-year survival was better in the VELCADE group when compared to dexamethasone: (hazard ratio 0.57, 95% CI 0.40-0.81, p=0.0013; hazard ratio 0.53, p=0.0005, respectively).
The Kaplan-Meier curves for survival for all patients is displayed in the following figure.

Figure 2.7.3-4 Kaplan-Meier Survival Curve (Study M34101-039, All Patients, ITT Population, N = 669)



Source: Module 5, M34101-039, section 14.5, Figure 14.2.4.1A and section 14.2, Table 14.2.4.1.
Note: Data for analysis censored on or before 13 January 2004; p-value from log-rank test adjusted by actual randomization stratification factors.

Response: time to response and duration of response.

Across all 627 patients included in the Response population, the overall response rate (CR+PR) was significantly higher (p-value <0.0001) for patients in the VELCADE treatment group (38%) compared to patients in the dexamethasone treatment group (18%).

The proportion of patients who achieved CR was also significantly higher (p-value=0.0001) in the VELCADE group (6%) compared to the dexamethasone group (<1%).

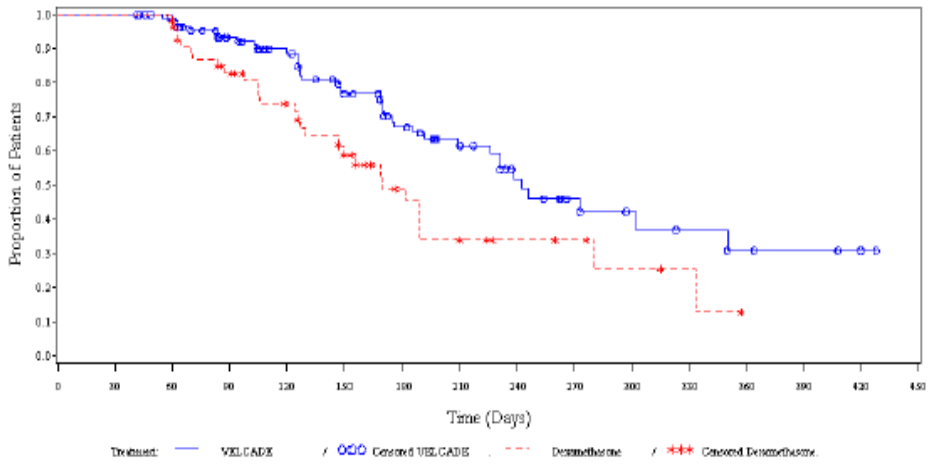
Time to first response (as the duration of time from date of first administration of study treatment to the date of first evidence of confirmed disease response) was similar between the VELCADE and dexamethasone groups while the duration of response, when analysed in the subgroup of 177 patients included in the Response Population who achieved a CR or PR, was longer for the VELCADE group.

Table 2.7.3-8 Summary of Best Confirmed Response to Treatment (Study M34101-039, Response Population, N = 627)

Best Confirmed Response	All Patients			Patients with 1 Prior Line of Therapy		
	VELCADE N (%) (n = 315)	Dexamethasone N (%) (n = 312)	p-value[a]	VELCADE N (%) (n = 128)	Dexamethasone N (%) (n = 110)	p-value[a]
CR+PR	121 (38)	56 (18)	<0.0001	57 (45)	29 (26)	0.0035
CR	20 (6)	2 (<1)	0.0001	8 (6)	2 (2)	
PR	101 (32)	54 (17)	<0.0001	49 (38)	27 (25)	
Near CR: IF+	21 (7)	3 (<1)		8 (6)	2 (2)	
MR	25 (8)	52 (17)		9 (7)	16 (15)	
CR+PR+MR	146 (46)	108 (35)		66 (52)	45 (41)	
No Change	137 (43)	149 (48)		50 (39)	48 (44)	
PD	22 (7)	41 (13)		9 (7)	12 (11)	
NE	10 (3)	14 (4)		3 (2)	5 (5)	

Source: Module 5, M34101-039, section 14.2, Table 14.2.5.1A and Table 14.2.5.6.
Note 1: Response based on computer algorithm using the protocol-specified EBMT criteria.
Note 2: percents calculated for the statistical output in section 14 of the CSR are 'rounded' to the nearest integer including percents ≥0.5% but <1% rounding to 1%; these are reported in the in text tables as <1%.
a P-value from the Cochran-Mantel-Haenszel chi-square test adjusted for the actual randomization stratification factors.

Figure 2.7.3-7 Kaplan-Meier Duration of Response Curve for All CR + PR Patients (Study M34101-039, N=177)



Other secondary efficacy endpoints: There was no significant difference between the treatment groups for time to first skeletal event (hazard ratio=0.76; p=0.3153), proportion of patients experiencing Grade 3 infections (p=0.188), and self-reported quality of life. On the other hands, significant increases in the self-reported symptom scores for nausea, vomiting and constipation were noted for VELCADE patients relative to dexamethasone patients.

Ancillary analyses

Several subgroup (exploratory), sensitivity and multivariate analyses were carried out for each of the primary and secondary more relevant outcomes (TTP, overall survival and response rate). In general, VELCADE significantly improved TTP, survival and response rate

- in patients who were reported by the investigator to be refractory to their last prior therapy (median TTP was 168 and 85 days in the VELCADE and dexamethasone groups,

respectively, for patients who were refractory (hazard ratio=0.49; p<0.0001) and 196 and 149 days, respectively for patients not (hazard ratio=0.71; p=0.0742);
- in patients who received more than one prior therapy (median TTP was 14.9 months and 2.9 months, respectively, in the VELCADE and dexamethasone groups for this patient subgroup (hazard ratio=0.55; p<0.0001);
- in patients who had received only one prior line of therapy (see table below).

Subgroup Analysis: Summary of Time to Disease Progression and Overall Survival (Days) for Patients who Received One and More than One Prior Line of Therapy (ITT Population, N = 669)

Analysis Subgroup	VELCADE (n = 333)	Dexamethasone(n=336)	Hazard Ratio (95% CI) p-valuea
Time to Progression			
Patients with one prior line			
N	132	119	0.56 (0.38, 0.81)
Median TTP (95% CI)	212 (188, 267)	169 (105, 191)	0.0021
Patients with 2 or more prior lines			
N	200	217	0.55 (0.41, 0.72)
Median TTP (95% CI)	148 (129, 192)	87 (84, 107)	<0.0001
Overall Survival			
Patients with one prior line			
N	132	119	0.42 (0.21, 0.85)
Median Overall Survival (95% CI)	NE (NE, NE)	NE (NE, NE)	0.0130
Patients with 2 or more prior lines			
N	200	217	0.63 (0.42, 0.94)
Median Overall Survival (95% CI)	504 (454, NE)	NE (465, NE)	0.0231

Note 1: Data for TTP analysis censored on or before 14 December 2003; date of progression determined by computer algorithm. Data for survival analysis censored on or before 13 January 2004.

Note 2: + denotes censored value; NE = not estimable.

Note 3: one patient in the ITT population had no prior therapy data recorded.

a p-value from log-rank test adjusted by actual randomization stratification factors except therapeutic history.

In the multivariate analysis, performed on the combined VELCADE and dexamethasone treatment groups, study treatment (i.e., treatment with VELCADE or dexamethasone) was a highly significant factor and treatment with VELCADE was correlated with a significantly longer time to progression, longer survival, higher response rate and longer duration of response compared to dexamethasone.

Analysis performed across trials (pooled analyses AND meta-analysis)

The key efficacy results for the phase 3 Study M34101-039 and for the phase 2 study M34100-025 were reviewed. However, Study M34101-039 and Study M34100-025 were intentionally designed to treat different patient populations, so the comparison of results between two studies is difficult.

Study M34101-039 enrolled patients who had received 1 to 3 prior therapies; the protocol eligibility criteria did not require patients to be refractory to therapy or to have exhausted all types of therapy. The patient population in this study represents a patient population at an earlier stage in their disease. Study M34100-025 was designed for patients who had relapsed following two or more prior therapies, and were refractory to their most recent therapy. The primary efficacy endpoint in Study M34101-039 was TTP and in Study M34100-025 was response rate. The results of the review are presented in the tables below.

Summary of Median Time to Disease Progression (Days) in Study M34101-039 and Study M34100-025 (ITT Population)

Study Population	N	Median TTP (days)	95% CI
Study M34101-039			
VELCADE, All Patients	333	189	148, 211
VELCADE, Pts with 1 Prior Line of Therapy	132	212	188, 267
VELCADE, Pts with >1 Prior Line of Therapy	200	148	129, 192
Dexamethasone	336	106	86, 128
Study M34100-025	202	213	154, 297

Note: Analysis conducted using Kaplan-Meier methods. In Study M34101-039: data for analysis censored on or before 14 December 2003; date of progression determined by computer algorithm.

Summary of Response Rates in Study M34101-039 and Study M34100-025 (Response Population)

Study Population	N	Response Rate (CR+PR) n (%)	95% CI
Study M34101-039			
VELCADE, All Patients	315	121 (38)	33, 44
VELCADE, Pts with 1 Prior Line of Therapy	128	57 (45)	36, 54
VELCADE, Pts with >1 Prior Line of Therapy	187	64 (34)	28, 42
Dexamethasone	312	56 (18)	14, 23
Study M34100-025	188	52 (28)	21, 35

Summary of Duration of Response (Days) in Study M34101-039 and Study M34100-025 (CR or PR Patients)

Study Population	N	Median Duration of Response (days)	95% CI
Study M34101-039			
VELCADE, All Patients	121	242	209, 350
VELCADE, Pts with 1 Prior Line of Therapy	57	246	231, NE
VELCADE, Pts with >1 Prior Line of Therapy	64	238	170, NE
Dexamethasone	56	169	147, 280
Study M34100-025	53	385	245, 538

Note 1: Analysis conducted using Kaplan-Meier methods. In Study M34101-039: data for analysis censored on or before 14 December 2003; date of progression determined by computer algorithm.

Note 2: + denotes censored value; NE = not estimable.

Note 3: the number of patients with CR/PR in Study M34100-025 based on the final clinical study report; includes one additional patient not assessed with CR or PR in the US Package Insert.

Supportive studies

The primary efficacy results from the RCT were supported by updates of two other Phase II trials (Study M34100-025 and M34100-024) presented in the original submission. Since that time, additional information are available in terms of time-to-event variables (TTP, duration of response and survival). In general, given the characteristics of the samples enrolled and studied (patients with multiple myeloma who had relapsed following 2 ore more prior therapy and progressing during last therapy) median TTP was similar in the original submission and in the updated data.
A further phase II, open-label extension study to provide PS-341 to patients who participated in the other 2 trials was also carried out and updated (M34101-029).

Study M34100-025 was an open-label, non-randomized, multi-center study conducted between February 2001 and June 2002 at 14 study centers in the US. Patients in this study received VELCADE at a dose of 1.3 mg/m2 administered as an IV bolus 2 times per week for 2 weeks (on Days 1, 4, 8, and 11) of a 21-day cycle; a maximum of up to 8 cycles of treatment could be administered. After Cycle 2, patients with progressive disease on VELCADE were allowed to have dexamethasone added to their treatment regimen. After Cycle 4, patients with no change in disease status on VELCADE also were

allowed to have dexamethasone added to the treatment regimen. Responding patients, or those felt to be deriving benefit, were allowed entry into the extension study M34100-029 to receive additional treatment with VELCADE alone or in combination with dexamethasone. A total of 202 patients were enrolled in this study.

Study M34100-024 was an open-label, randomized (non-comparative), multi-center study conducted between May 2001 and July 2002 at 10 centers in the US. This study was designed to explore the efficacy and safety of two doses of VELCADE, 1.0 mg/m2 and 1.3 mg/m2, in patients with multiple myeloma who had failed to respond to or had relapsed following either conventional or high-dose front-line therapy. Patients received VELCADE at a dose of 1.0 or 1.3 mg/m2 based on random allocation administered as an IV bolus 2 times per week for 2 weeks (on Days 1, 4, 8, and 11) of a 21-day cycle; a maximum of up to 8 cycles of treatment could be administered. As in Study M34100-025, dexamethasone could be added if the response to VELCADE monotherapy was inadequate. Responding patients and those deriving benefit were allowed entry into the extension study *M34100-029* to receive additional VELCADE. A total of 54 patients were enrolled in this study.

The following table presents a synthesis of the updates for both studies:

Table 2.5.4-6 Updated Time to Event Analysis for the Phase 2 Studies M34100-025 and M34100-024

	M34100-025 1.3 mg/m^2 (N=202)		M34100-024			
			1.0 mg/m^2 (N=28)		1.3 mg/m^2 (N=26)	
Median, days (months)	**Original Submission**	**Updated Data**	**Original Submission**	**Updated Data**	**Original Submission**	**Updated Data**
Duration of follow-up	303 (10.0)	700 (23.0)	288 (9.5)	796 (26.2)	245 (8.1)	794 (26.1)
TTP	210 (6.9)	213 (7.0)	NE	127 (4.2)	321 (10.6)	357 (11.7)
Overall Survival	478 (15.7)	518 (17.0)[a]	NE	813 (26.7)	NE	NE
Duration of Response	365 (12.0)[b]	385 (12.7)[b]	NE[b]	NE[b]	NE[b]	608 (20.0)[b]

Source: Module 5, Addendum M34100-025, Addendum M34100-024

a Median overall survival in the EU submission based on an interim analysis of data was 17.5 months.

b Based on number of patients with CR or PR: N=53 in M34100-025; N=8 for 1.0 mg/m^2 in M34100-024 and N=10 for 1.3 mg/m^2 in M34100-024

The overall response rate, ORR (CR+PR+MR; CR+PR), appears to be higher in study 024, which enrolled less advanced patients. The time to event analyses of this study are inconclusive mainly because of the small number of patients, because the majority of patients were censored in the duration of response and time to progression analyses, and because median survival and the median duration of response had not been reached in either dose group (median duration of follow was 9.5 and 8 months in the two groups).

Study M34101-029 is a Phase 2 extension study designed to allow for the continued administration of bortezomib to patients who were eligible for and previously participated in a Phase 1 or 2 bortezomib clinical study sponsored by MPI, achieved a clinical benefit on bortezomib, and in the investigator's opinion could benefit from further therapy with bortezomib. The study also provides for retreatment of selected patients. The Phase 1 and 2 studies contribute patients to M34101-029 with hematologic malignancies including multiple myeloma and chronic lymphocytic leukemia and patients with solid tumors including prostate, pancreatic, lung, and colon cancers. In these studies bortezomib can be administered alone or in combination with dexamethasone, irinotecan, gemcitabine, or docetaxel, depending on the individual parent protocol from which the patients enter. The data collected will be used to update the time to event analyses for the phase 2 multiple myeloma studies, M34100-024 and M34100-025. The applicant will present these analyses in a separate report.

M34101-040 is an additional International, Non-Comparative, Open-Label Study of PS-341 Administered to Patients with Multiple Myeloma Who Received High-dose Dexamethasone in Millennium Protocol M34101-039 or Experienced Progressive Disease after Receiving at Least Four Previous Therapies.

As of 31 March 2004, efficacy data had not been analyzed in this ongoing study. The response rate to treatment with bortezomib tends to be higher in patients earlier in the course of their disease. The response rate was 45% in Study M34101-039 patients who received only 1 prior line of therapy, 34% in Study M34101-039 patients who had received more than 1 prior line of therapy, and 28% in Study M34100-025 (refractory patients who had received 2 or more prior therapies). The response rates to bortezomib in all three populations were superior to the 18% response rate to dexamethasone observed in Study M34101-039.

Discussion on Clinical Efficacy

The clinical efficacy of VELCADE for the current indication is mainly based on a large, well-designed and well conducted RCT where VELCADE and an acceptable alternative regimen (high dose dexamethasone) were compared in terms of TTP. The benefit of VELCADE was also supported by secondary endpoints, such as overall and 1-year survival, response rate, duration of response, etc. Pre-planned subgroups, exploratory and sensitive analyses do support the efficacy of VELCADE across several strata representative of the heterogeneity of the sample studied (patients with multiple myeloma, who received at least one prior therapy and requiring a further line of therapy because on progression or relapsing after last therapy).

The median number of prior therapeutic lines administered was 2 in both treatment groups with a range of 1 to 8. Almost 40% of all patients had received only one prior line of therapy, including 40% of patients in the bortezomib group and 35% of patients in the dexamethasone group. Overall, 98% of patients had received prior treatment with steroids, 91% had received prior alkylating agent therapy, 77% of patients had received prior anthracyclines, 67% had received prior stem cell transplant or other high dose therapy, and 49% had received prior thalidomide. Review of baseline prior high-dose steroid therapy revealed that 60 patients (9%) might have been refractory to dexamethasone.

Among those patients who had received only one prior line of therapy, 85% had received treatment with alkylating agents, 71% had received treatment with anthracyclines, 62% had received prior stem cell transplant or other high dose therapy and 21% had received prior therapy with thalidomide. A total of 96% of the patients who had received one prior line of therapy had received prior treatment with steroids in combination with other chemotherapeutics. A total of 95% had received anthracyclines and/or an alkylating agent as their only prior therapy.

In terms of time to progression, overall survival, overall response rate, median duration of response, the activity of bortezomib appears clinically relevant. Median TTP was 189 days (6.2 months) for bortezomib and 106 days (3.5 months) for dexamethasone. The likelihood of survival at one year was 80% on bortezomib and 66% on dexamethasone ($p=0.0025$), representing a 41% decrease in the risk of death in the first year on bortezomib treatment. The overall response rate (CR+PR) was significantly higher for patients in the bortezomib group (38%) compared to patients in the dexamethasone group (18%), $p<0.0001$. The median duration of response for bortezomib patients with CR or PR was 242 days (8.0 months) and was 302 days (9.9 months) for patients who achieved CR in the bortezomib group.

Median time to response was rapid occurring at 43 days in both treatment groups. No differences were noted between the bortezomib and dexamethasone treatment groups for time to skeletal event.

For patients who had received only one prior therapeutic line, median TTP (7.0/5.6 months), overall survival, overall response rate (45%/ 26%) were significantly better in the bortezomib group compared to the dexamethasone group.

The response rate to treatment with bortezomib tends to be higher in patients earlier in the course of their disease. The response rate was 45% in Study M34101-039 patients who received only 1 prior line of therapy, 34% in Study M34101-039 patients who had received more than 1 prior line of therapy, and 28% in Study M34100-025 (refractory patients who had received 2 or more prior therapies). The

response rates to bortezomib in all three populations were superior to the 18% response rate to dexamethasone observed in Study M34101-039.

Although the two arms are well balanced in terms of relevant prognostic factors (related to socio-demographic characteristics, disease and prior therapy), and the VELCADE yield does not change across strata, the presence of a patient sub-group (251, 38%) receiving only one prior therapy (and have not received stem-cell transplant/high dose therapy) suggests caution regarding the current VELCADE place in therapy. The available data demonstrate that VELCADE has efficacy as a (second-line) treatment for progressing/relapsed multiple myeloma patients (who received at least one prior line of therapy). The present findings do not support the indication as first-line treatment (induction therapy), or for any consolidation or maintenance therapy, and for any type of combination therapy. In addition, VELCADE use should not be considered in patients who have received only one prior therapy and are eligible for stem-cell transplant/high dose therapy. Besides eligibility for transplantation, in patients who have received only one prior therapy the kind of prior therapy and the type and time of relapse/progression should be considered too.

In conclusion, the totality of the data from the phase 2 and phase 3 studies supports the efficacy of bortezomib in myeloma patients who have received at least one prior therapy. Bortezomib has demonstrated superior efficacy, including improved survival compared to standard therapy in the setting of the largest phase 3 randomized study conducted to date in patients with relapsed myeloma.

Clinical Safety

The safety profile of VELCADE is based on the previous experience with single-agent VELCADE in two phase 2 clinical studies (Studies M34101-029 and M34101-040) and on the large, international, randomized phase 3 study (Study M34101-039) in which VELCADE was compared to high-dose dexamethasone.

In the phase 3 study, safety was closely monitored particularly for the events reported in the Table below:

MedDRA SOC	Event
Cardiac disorders	Heart Failure
	Ischaemic Events: myocardial infarction, angina
	Arrhythmias
Gastrointestinal disorders	Ileus paralytic
	Intestinal obstruction
	Pancreatitis
Immune system disorders	Acute hypersensitivity
	Immune complex disorders
	Serum sickness
	Glomerulonephritis
	Amyloidosis
Nervous system disorders	Central Neurotoxicity
	Encephalopathy
	Dementia
	Parkinson's disease
	Seizures
	Psychosis
	Mental status changes / confusion
	Depression
Hepatic disorders	Hepatitis / liver function test abnormalities
Vascular disorders	Hypotension
	Hemorrhage

In the previous phase 2 clinical studies, VELCADE was associated with painful peripheral sensory, generally with Grade 1 or 2 in intensity, more frequent in those patients who had previously received neurotoxic therapy and those with preexisting neuropathy. VELCADE was also associated with a high incidence of fatigue and gastrointestinal disorders, primarily reports of diarrhea, constipation, and nausea with or without vomiting. Finally, VELCADE was associated with thrombocytopenia and neutropenia, although severe myelosuppression and febrile neutropenia were not very common.

Patient Exposure

In addition to the (~600) patients who had been exposed to VELCADE in all clinical studies at the time of the original Marketing Authorisation Application, more than 800 patients have been exposed to VELCADE in the clinical studies that contributed safety data to this application (Studies M34101-039, -040, and -029).

It is estimated that as of 12 May 2004 more than 6,000 patients have been treated with VELCADE, based on clinical study and post-marketing experience.

In the phase 3 study *M34101-039*, compliance with both the VELCADE and dexamethasone dosing regimens was excellent. On average, VELCADE patients received 95% of the expected dose in Cycle 1, and 72% or more of the expected dose at all subsequent cycles. Thirty-four percent of VELCADE patients received treatment in all 8 cycles of twice weekly therapy. Over all cycles, the mean number of VELCADE doses delivered per cycle ranged from 3.6 to 3.9 out of a maximum of 4. Similarly, for dexamethasone the mean number of doses delivered per cycle in the first 4 cycles ranged from 11.0 to 11.4 out of a maximum of 12, and the mean number delivered in Cycle 5 and beyond ranged from 3.8 to 4.1 out of a maximum of 4. Exposure to study treatment was similar between the treatment groups. In the VELCADE group 56%, 29%, and 9% of patients completed (i.e., received 3 of 4 doses in each cycle) 5, 8, and 11 cycles (15, 24 and 39 weeks, respectively), and in the dexamethasone group 56%, 28% and 5% of patients completed 3, 5 and 9 cycles (15, 24 and 40 weeks, respectively).

The extension study *M34101-029* provided an opportunity for patients with multiple myeloma who had received benefit from VELCADE therapy on other studies to receive additional VELCADE treatment. The 63 patients who were treated in the phase 2 studies, M34100-025 and M34100-024, and enrolled onto M34101-029 represent the group of myeloma patients exposed to the longest duration of VELCADE therapy in a clinical study setting. The mean total duration of VELCADE treatment in these 63 patients was ~50 weeks (range 23 to 100 weeks), and the mean number of cycles was 15 (range 7 to 32). This is a substantially more extensive exposure than is available from the phase 3 study, in which a maximum of 40 weeks of therapy was allowed, and to date only 31 patients have received 40 weeks of therapy.

Study *M34101-040*, the companion study to the phase 3 study M34101-039, is ongoing. As of the data cut-off used for reporting of serious adverse event information for this submission, a total of 437 patients had received treatment with VELCADE. No data regarding extent of VELCADE exposure are currently available from this study.

Pivotal study

Study M34101-039: An International, Multi-Center, Randomized, Open-Label Study of PS-341 Versus High-Dose Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

A total of 663 patients were included in the safety population, 331 patients in the bortezomib group and 332 patients in the dexamethasone group.

Adverse events

The incidence of adverse events was high, with almost all patients experiencing at least 1 treatment-emergent adverse event during the study.

The overall incidence of adverse events was similar in the bortezomib and dexamethasone groups, with 100% (331 of 331 patients) and 98% (327 of 332 patients) of patients in the bortezomib and dexamethasone groups, respectively, experiencing at least 1 treatment-emergent adverse event during the study. The incidence of Grade 4 adverse events was 14% (45 of 331 patients) and 16% (52 of 332 patients) in the bortezomib and dexamethasone groups, respectively. Among the 331 bortezomib-

treated patients, the incidence of Grade 4 adverse events was 45 patients (14%). Grade 4 adverse events reported for >1% of patients in the bortezomib group included thrombocytopenia (12 patients; 4%), neutropenia (8 patients; 2%), and hypercalcemia (5 patients; 2%). Among the 332 patients in the dexamethasone group, the incidence of Grade 4 adverse events was 16% (52 patients); the only Grade 4 adverse events reported for >1% of patients was hyperglycemia NOS (7 patients; 2%).

Serious adverse events were 44% (144 of 331 patients) and 43% (144 of 332 patients) in the bortezomib and dexamethasone groups, respectively, and adverse events leading to discontinuation were 37% (121 of 331 patients) and 29% (96 of 332 patients) in the bortezomib and dexamethasone groups, respectively.
A higher incidence of ≥Grade 3 adverse events was seen in the bortezomib group (248 of 331 patients; 75%) compared to the dexamethasone group (198 of 332 patients; 60%). More patients in the bortezomib group (324 of 331 patients; 98%) than in the dexamethasone group (297 of 332 patients; 89%) experienced at least 1 adverse event that was considered by the investigator to be study drug-related.

Among the 331 bortezomib-treated patients, the most commonly reported adverse events overall were diarrhea and nausea (190 patients each; 57%), fatigue and constipation (140 patients each; 42%), peripheral neuropathy NEC (120 patients, 36%), vomiting NOS (117 patients; 35%), pyrexia (116 patients; 35%), thrombocytopenia (115 patients; 35%), anemia NOS (87 patients; 26%), headache NOS (85 patients; 26%), anorexia (75 patients; 23%), cough (70 patients; 21%) and paresthesia (68 patients; 21%). These adverse events were among the most commonly reported adverse events in a phase 2 study, M34100-025 and the incidence rates of these adverse events seen were generally similar. Fifty-eight (18%) of 331 bortezomib-treated patients experienced a Grade 3 gastrointestinal disorder. The only Grade 4 gastrointestinal disorder reported among bortezomib-treated patients was gastrointestinal hemorrhage NOS, which was reported for 2 (<1%) of 331 patients. The incidence of serious gastrointestinal disorders among bortezomib-treated patients was 30 of 331 patients (9%) and the incidence of gastrointestinal disorders leading to study discontinuation was 21 of 331 patients (6%).

The most commonly reported adverse events among the 332 patients in the dexamethasone group were fatigue (106 patients; 32%), insomnia (90 patients; 27%), anemia NOS (74 patients; 22%) and diarrhea (69 patients; 21%).

The rate of ≥Grade 3 adverse events was with three-fourths (75%) of bortezomib treated patients and 60% of dexamethasone-treated patients experiencing at least 1 ≥Grade 3 adverse event. In the bortezomib group, the ≥Grade 3 adverse events occurring at an incidence >10% were thrombocytopenia (97 patients; 29%) and neutropenia (48 patients; 15%).

The only ≥Grade 3 adverse event that occurred at an incidence >10% among the 332 dexamethasone-treated patients was anemia NOS (35 patients; 11%).

The incidence of peripheral neuropathy NEC was 36% (120 of 331 patients) among bortezomib-treated patients and was considered by the investigator to be study drug-related (115 of 331 patients; 35%). Peripheral neuropathy NEC was ≥Grade 3 in intensity for 26 (8%) of 331 patients, and was reported as a serious adverse event for 4 (1%) of 331 patients. Bortezomib was discontinued because of peripheral neuropathy NEC for 27 (8%) of 331 patients. Reversibility of treatment-emergent ≥Grade 2 peripheral neuropathy NEC was seen for approximately half (51%) of patients who experienced this event. The median time to resolution of or improvement in peripheral neuropathy NEC was 107 days.

Overall, 39 patients, 14 (4%) of 331 patients in the bortezomib group and 25 (8%) of 332 patients in the dexamethasone group, died within 30 days after the last study drug dose or died >30 days after the last study drug dose due to a cause that was considered to be study drug related.

In both treatment groups, the most commonly reported cause of death was disease progression, reported as the cause of death for 5 (2%) of 331 patients and 7 (2%) of 332 patients in the bortezomib

and dexamethasone groups, respectively. The cause of death was considered by the investigator to be study drug-related for a total of 9 patients, 4 (<1%) patients in the bortezomib group and 5 (2%) in the dexamethasone group. In the bortezomib group, the causes of deaths were cardiac arrest, cardiogenic shock, congestive heart failure, and respiratory insufficiency (1 patient each). In the dexamethasone group, causes of death that were considered to be study drug-related included sepsis (2 patients) and bacterial meningitis and cardiorespiratory arrest (1 patient each); for the remaining patient, who experienced sudden death at home, the exact cause of death was unknown.

The reported incidence and the types of serious adverse events were similar between the treatment groups, 44% and 43% in the bortezomib and dexamethasone groups, respectively. In both groups, serious events were most commonly reported in the Infections and Infestations SOC (most commonly pneumonia and sepsis), 42 (13%) patients in the bortezomib-group and 58 (17%) patients in the dexamethasone group. Commonly reported serious events in the bortezomib treatment group were pyrexia (6%), diarrhea NOS (5%), dyspnea NOS (4%), and vomiting NOS (3%); all other serious events were reported ≤2%. In the dexamethasone treatment group, commonly reported serious events were pneumonia NOS (22 patients; 7%), pyrexia (4%) and hyperglycemia (3%); all other serious events were reported in 2% of patients or fewer.

One patient in the bortezomib treatment group had torsades de pointes reported as a treatment-emergent adverse event. The event was Grade 4 in severity, serious in nature and assessed as possibly related to study treatment. Upon further review, the torsade de pointes was considered to be caused by sotalol intoxication due to the patient's renal insufficiency.

As drug-related assessed by the investigator were 24% (80 of 331 patients) of serious adverse events in the bortezomib group and 25% (83 of 332 patients) in the dexamethasone groups.
The most commonly reported drug-related serious events in the bortezomib treatment group were diarrhea NOS (11 patients, 3%); pyrexia (7 patients, 2%); dehydration, dyspnea NOS, nausea and vomiting NOS (6 patients each, 2%); Herpes zoster and thrombocytopenia (5 patients each, 2%); and neutropenia and peripheral neuropathy NOS (4 patients each, 1%).

Among patients treated with bortezomib, 196 (59%) missed at least one dose due to an adverse event and 141 (43%) had a dose reduction due to adverse events. In the dexamethasone treatment group, 83 (25%) and 45 (14%) patients, respectively, missed doses or had dose reductions due to adverse events. The most commonly reported events leading to missed doses and dose reductions in the bortezomib treatment group were peripheral neuropathy NEC, thrombocytopenia, neutropenia and diarrhea.

The most commonly reported treatment-emergent adverse events leading to discontinuation in the bortezomib group, regardless of relationship to study drug, were peripheral neuropathy NEC reported in 27 (8%) patients; diarrhea NOS, nausea and thrombocytopenia reported in 8 (2%) patients each; spinal cord compression, vomiting NOS and hypercalcemia reported in 7 (2%) patients each, fatigue reported in 6 patients (2%) and neuralgia and dyspnea NOS reported in 4 (1%) patients each.

In the dexamethasone treatment group, the most commonly reported events leading to treatment withdrawal, regardless of relationship to study treatment, were psychotic disorder NOS and hyperglycemia NOS reported in 7 (2%) patients each, thrombocytopenia reported in 6 (2%) patients, disease progression NOS reported in 5 (2%) patients, and headache NOS, arthralgia, depression NOS, anemia NOS, and congestive cardiac failure reported in 4 (1%) patients each.

84 (25%) of 331 patients in the bortezomib treatment group and 61 (18%) of 332 patients in the dexamethasone treatment group were discontinued from treatment due to adverse events assessed as drug-related by the investigators. In bortezomib group, the most commonly reported drug-related event leading to discontinuation was peripheral neuropathy NEC reported in 27 (8%) patients. Other drug related events were thrombocytopenia, nausea and diarrhea NOS (7 patients each, 2%), fatigue (6 patients, 2%), vomiting NOS (5 patients, 2%) and neuralgia NOS (4 patients, 1%).

Treatment-Emergent Adverse Events Reported by ≥10% of VELCADE treated Patients, by MedDRA Preferred Term (Safety Population; N=663)

	Treatment Group	
MedDRA SOC / Preferred Term	VELCADE (N=331) n (%)	Dexamethasone (N=332) n (%)
At least 1 adverse event	331 (100)	327 (98)
Diarrhoea NOS	190 (57)	69 (21)
Nausea	190 (57)	46 (14)
Fatigue	140 (42)	106 (32)
Constipation	140 (42)	49 (15)
Vomiting	117 (35)	20 (6)
Pyrexia	116 (35)	54 (16)
Thrombocytopenia	115 (35)	36 (11)
Anaemia NOS	87 (26)	74 (22)
Peripheral neuropathy NOS	86 (26)	20 (6)
Headache NOS	85 (26)	43 (13)
Anorexia	75 (23)	14 (4)
Cough	70 (21)	35 (11)
Paraesthesia	68 (21)	27 (8)
Dyspnoea NOS	65 (20)	58 (17)
Neutropenia	62 (19)	5 (2)
Rash NOS	61 (18)	20 (6)
Insomnia	60 (18)	90 (27)
Abdominal pain NOS	53 (16)	12 (4)
Bone pain	52 (16)	50 (15)
Pain in limb	50 (15)	24 (7)
Back pain	46 (14)	33 (10)
Dizziness (excl. vertigo)	45 (14)	34 (10)
Arthralgia	45 (14)	35 (11)
Nasopharyngitis	45 (14)	22 (7)
Muscle cramps	41 (12)	50 (15)
Appetite decreased NOS	42 (13)	17 (5)
Herpes zoster	42 (13)	15 (5)
Weakness	40 (12)	40 (12)
Peripheral sensory neuropathy	40 (12)	7 (2)
Myalgia	39 (12)	18 (5)
Rigors	37 (11)	8 (2)
Oedema lower limb	35 (11)	43 (13)
Asthenia	34 (10)	23 (7)

NEC=Not elsewhere classified NOS=not otherwise specified.

Serious adverse events and deaths

Within 30 days of the last dose of study treatment were 12 (4%) deaths in the bortezomib treatment group and 23 (7%) deaths in the dexamethasone treatment group.

14 (4%) of 331 patients in the bortezomib group and 25 (8%) of 332 patients in the dexamethasone group, died within 30 days after the last study drug dose or died >30 days after the last study drug dose due to a cause that was considered to be study drug related. The cause of death was considered by the

investigator to be study drug-related for a total of 8 patients, 4 (1%) of 331 patients in the bortezomib group and 4 (1%) of 332 patients in the dexamethasone group.

Study Drug-Related Deaths, by Treatment Group

Patient Number	Age (years)	Sex	Cause of Death (Per Millennium Product Safety)	Days Post Treatment	Total Number of Study Drug Doses
VELCADE					
034-011	59	Female	Cardiogenic shock	2	10
061-027	62	Male	Respiratory insufficiency	38	9
115-002	65	Male	Congestive heart failure	62	26
180-012	72	Male	Cardiac arrest	16	12
Dexamethasone					
011-004	77	Male	Septicemia, bilateral pneumonia	3	20
061-011	69	Male	Bacterial meningitis	39	8
061-012	60	Male	Sudden death (cause unknown)	6	31
061-019	59	Male	Pneumococcal sepsis	1	7

Overall, the most commonly reported cause of death on study was disease progression, with 12 patients, 5 (2%) of 331 patients in the bortezomib group and 7 (2%) of 332 patients in the dexamethasone group having disease progression reported as the primary cause of death. Two (<1%) patients in the bortezomib group and 8 (2%) patients in the dexamethasone group, had sepsis or other infection reported as the primary cause of death on study.

In the dexamethasone group, sepsis or septic shock was reported as a cause of death for 5 patients. For 2 of these 5 patients, sepsis was considered to be study drug-related; for the remaining 3 patients, sepsis was considered to have no relationship to study drug. An infection other than sepsis was reported as a cause of death for 3 additional patients in the dexamethasone group (bronchopneumonia, bacterial meningitis, pneumonia). Bacterial meningitis was considered to be study drug-related for one patient, for the remaining 2 patients, the infection was considered to have no relationship to study drug.
Five patients, 3 (<1%) patients in the bortezomib group and 2 (<1%) patients in the dexamethasone group died due to a respiratory event.

The reported incidence and the types of serious adverse events were similar between the treatment groups; a total of 144 (44%) of the 331 patients in the bortezomib treatment group and 144 (43%) of 332 patients in the dexamethasone treatment group experienced at least one treatment-emergent serious adverse event. In both groups, serious events were most commonly reported in the Infections and Infestations SOC, occurring in 43 (13%) of the 331 bortezomib-treated patients and 58 (17%) of the 332 dexamethasone-treated patients. The most commonly reported infections that were serious in nature were pneumonia and sepsis. General disorders and administration site conditions, most commonly reports of pyrexia, were reported as serious events in 43 (13%) and 36 (11%) patients in the bortezomib and dexamethasone groups, respectively.

The most commonly reported serious events in the bortezomib treatment group were pyrexia (6%), diarrhea NOS (5%), dyspnea NOS and pneumonia NOS (4% each), and vomiting NOS (3%). In the dexamethasone treatment group, the most commonly reported serious events were pneumonia NOS (7%), pyrexia (4%) and hyperglycemia (3%).

A similar proportion of patients in the 2 treatment groups experienced serious adverse events that were assessed as drug-related by the investigators, including 80 (24%) of 331 patients in the bortezomib treatment group and 83 (25%) of 332 patients in the dexamethasone treatment group.

Serious drug-related adverse events in the bortezomib treatment group were most commonly reported in the gastrointestinal disorders SOC, with 20 patients (6%) experiencing serious drug-related events. A total of 17 (5%) bortezomib-treated patients experienced drug-related serious events in the general disorders and administration site conditions SOC and 15 patients each (5%) experienced events in the infections and infestations SOC and cardiac disorders SOC. The most commonly reported drug-related serious events in the bortezomib treatment group were diarrhea NOS (11 patients, 3%); pyrexia (7 patients, 2%); dehydration, dyspnea NOS, nausea and vomiting NOS (6 patients each, 2%); herpes zoster and thrombocytopenia (5 patients each, 2%); and neutropenia and peripheral neuropathy NOS (4 patients each, 1%). Serious drug-related adverse events in the dexamethasone treatment group were most commonly reported in the infections and infestations SOC, with 33 patients (10%). A total of 16 dexamethasone-treated patients (5%) experienced serious drug-related events in the metabolism and nutrition disorders SOC. The most commonly reported drug-related serious events in the dexamethasone treatment group were pneumonia NOS (13 patients, 4%), hyperglycemia NOS (11 patients, 3%), and psychotic disorder and pyrexia (6 patients each, 2%).

Laboratory findings

Comparison of safety profiles of dexamethasone and bortezomib reveals expected findings. Metabolic adverse events, e.g. hyperglycaemia, were more frequently reported in the dexamethasone group.

Among patients with NCI CTC Grade 0, 1 or 2 WBC at baseline, 51 (16%) of 328 in the bortezomib treatment group and 10 (3%) of 329 in the dexamethasone treatment group experienced Grade 3 or 4 leukopenia as a worst on-study value. Among those patients with Grade 0, 1 or 2 ANC and ALC at baseline, 78 (25%) of 315 and 105 (33%) of 315, respectively, in the bortezomib treatment group and 15 (5%) of 324 and 81 (25%) of 319, respectively, in the dexamethasone treatment group experienced Grade 3 or 4 neutropenia or Grade 3 lymphopenia, respectively, during the study.

Grade 3 or 4 anemia occurred in 50 (16%) of 321 and 34 (11%) of 317 patients in the bortezomib and dexamethasone treatment groups, respectively, who had Grade 0, 1 or 2 hemoglobin levels at baseline. For platelet count, among the 323 patients in the bortezomib treatment group with Grade 0, 1 or 2 platelet counts at baseline, 125 (39%) had at least one report of Grade 3 or 4 thrombocytopenia during the study compared to 30 (9%) of 323 patients in the dexamethasone treatment group.

A shift from baseline to a worst value on study of Grade 4 leukopenia, neutropenia, anemia or thrombocytopenia were reported in 4 (1%), 15 (5%), 5 (2%), and 11 (3%), respectively, of the bortezomib -treated patients with baseline and post-baseline results for each laboratory parameter. In the dexamethasone treatment group Grade 4 leukopenia, neutropenia, anemia or thrombocytopenia were reported in 2 (<1%), 3 (<1%), 6 (2%), and 4 (1%) patients, respectively, with baseline and post-baseline results for each laboratory parameter.

A total of 11 bortezomib-treated patients had platelet counts $<10\times10^9$/L during the study. In the bortezomib group, thrombocytopenia was reported in 115 (35%) of the 331 patients and was Grade 3 or 4 in severity in 97 patients (29%) and serious in nature in 5 (2%); thrombocytopenia led to discontinuation of bortezomib in 8 patients (2%). In the dexamethasone treatment group, thrombocytopenia was reported as a treatment-emergent adverse event in 36 (11%) of the 332 patients; the event was Grade 3 or 4 in severity in 7% of patients. The reported incidence of thrombocytopenia that was serious in nature or that led to discontinuation in the dexamethasone group (2%) was similar to the incidence reported in the bortezomib group.

Neutropenia was reported as a treatment-emergent adverse event in 62 (19%) of the 331 bortezomib-treated patients and 5 (2%) of the 332 dexamethasone-treated patients. A higher proportion of patients were also reported to have Grade 3 or 4 neutropenia in the bortezomib treatment group (48 patients, 15%) compared to the dexamethasone treatment group (4 patients, 1%). Four reports in the bortezomib treatment group, were listed as serious in nature and none of the patients discontinued treatment due to neutropenia. There was one reported case of febrile neutropenia in the bortezomib treatment group.

The reported incidence of anemia as a treatment-emergent adverse event was similar across the 2 treatment groups (26% and 22% in the bortezomib and dexamethasone treatment groups, respectively), as was the incidence of Grade 3 or 4 anemia, as a serious event and as an event leading to discontinuation.
Leukopenia NOS was reported in 7% and 2% of patients in the bortezomib and dexamethasone treatment groups, respectively; the incidence of Grade 3 or 4 leukopenia NOS was 4% and 1%, respectively. Lymphopenia was reported in 5% and 2% of patients in the bortezomib and dexamethasone groups, respectively, and the incidence of Grade 3 or 4 lymphopenia was 4% and 2%, respectively. One patient (<1%) in the bortezomib group discontinued the study due to leukopenia.

The most common clinical chemistry abnormality that was reported as an adverse event was hyperglycemia NOS, reported in 54 patients overall, including 5 (2%) of 331 bortezomib patients and 49 (15%) of 332 dexamethasone patients; the event was Grade 3 or 4 in severity in 28 (8%) of the 332 dexamethasone-treated patients and serious in nature in 11 (3%). The most commonly reported clinical chemistry abnormality in the bortezomib treatment group was hypokalemia, reported in 22 (7%) of the 331 patients; a similar proportion of patients in the dexamethasone treatment group had hypokalemia reported as an adverse event (16 patients, 5%). Hypocalcemia and hypercalcemia were reported in 12 (4%) and 13 (4%) patients, respectively, in the bortezomib treatment group and in 20 (6%) and 3 (<1%) patients, respectively, in the dexamethasone treatment group. These events were reported as Grade 3 or 4 in severity, serious in nature and led to discontinuation in ≤2% of patients. Blood creatinine increased, hyponatremia, hypoglycemia NOS, blood alkaline phosphatase increase NOS, ALT increased, AST increased, hyperuricemia and hyperkalemia were reported in a similar number of patients in each treatment group.

In the bortezomib treatment group, only small mean changes were noted over time for each of the serum electrolytes and glucose.

Mean changes in creatinine clearance from baseline to last assessment on study were increases of 11.0 and 13.4 μmol/L in the bortezomib and dexamethasone treatment groups, respectively.
Small mean changes, primarily decreases from baseline, were noted for AST and ALT in the bortezomib treatment group.

At the last assessment on study, mean alkaline phosphatase had increased 4.9 U/L in the bortezomib treatment group.

At the last assessment on study, mean bilirubin had increased 1.1 μmol/L.

Vital signs
Hypotension, including the MedDRA preferred terms hypotension NOS, postural hypotension, and orthostatic hypotension, was reported as an adverse event for 38 (11%) of 331 patients in the bortezomib group and 6 (2%) of 332 patients in the dexamethasone group.

Safety in special populations

Analyses comparing the incidence of adverse events overall, Grade 3 or 4 adverse events, serious adverse events, and adverse events leading to discontinuation by sex, age, race, baseline body surface area, baseline creatinine clearance, baseline liver function, myeloma subtype (IgA, IgG, or light chain/other), and number of prior lines of therapy (1 versus >1) did not reveal any clinically relevant differences based upon these demographic and baseline factors.

In the bortezomib group, the incidence of Grade 3 and 4 adverse events, serious adverse events, and adverse events leading to discontinuation was lower among patients aged <50 years than among those aged 51 years or older. There were no notable differences among age groups with regard to these adverse event categories in the dexamethasone group.

In the bortezomib group the incidences of serious adverse events and adverse events leading to bortezomib discontinuation were higher in males than in females.

In both treatment groups Grade 3 and 4 adverse events were more common in patients with a BSA >2 m^2. In the bortezomib group serious adverse events were more common in patients with a BSA >2 m^2. In the bortezomib group, a difference was seen by baseline creatinine clearance with regard to the incidence of metabolic and nutrition disorders and vascular disorders, with a higher incidence of such events seen among patients with impaired renal function (creatinine clearance ≤50 mL/min).

Among the bortezomib-treated patients, a higher incidence of metabolism and nutrition disorders, psychiatric disorders, anorexia, dehydration, hypokalemia, and insomnia was seen among patients who had previously received thalidomide for ≥12 months compared to those who received thalidomide for <12 months or had not received thalidomide.

In the bortezomib group, the incidence of adverse events leading to discontinuation and the incidence of metabolism and nutrition disorders was higher among patients who did not receive prior high-dose therapy compared to those who did.

40 (12%) patients in the bortezomib group and 28 (8%) patients in the dexamethasone group received >10 mg/day prednisone or equivalent, which is considered protocol violation. However, this has not confounded the efficacy results as these patients were censored in the efficacy analysis at the last documented visit date at which study assessments indicated that the patient was stable or improving.

In the bortezomib group 23% of patients who received oral hypoglycemic therapy and 1% of patients who did not receive such therapy experienced hypoglycemia. In contrast, in the dexamethasone group 2% of patients who received oral hypoglycemic therapy and 1% of patients who did not receive such therapy experienced hypoglycemia. Concomitant treatment with an oral hypoglycemic during bortezomib therapy may be associated with an increased risk of hypoglycemia. A warning is currently included in the prescribing information with regard to this risk.

Data from non-randomized, phase 2 studies suggested that heart failure events in bortezomib treated patients were more common in patients with pre-existing heart failure. Therefore, adverse events were analyzed according to treatment with an angiotensin inhibitor (ACE inhibitor or angiotensin receptor blocker) in combination with a diuretic at baseline. A total of 25 (8%) patients in the bortezomib group and 17 (5%) patients in the dexamethasone group were using an angiotensin inhibitor in combination with a diuretic at baseline. In both the bortezomib and dexamethasone groups the incidence of cardiac events was higher in patients using an angiotensin inhibitor in combination with a diuretic at baseline, and they suggest that patients with heart failure at baseline were more likely to report heart failure as an adverse event on the current study.

Immunological events

Not Applicable.

Safety related to drug-drug interactions and other interactions

Not Applicable.

Discontinuation due to AES

Patients in the VELCADE group were more likely to have missed doses or to have dose reductions due to adverse events than patients in the dexamethasone group. Among the VELCADE patients, 59% missed at least one dose due to an adverse event and 43% had a dose reduction. In the dexamethasone treatment group, 25% and 14% of patients, respectively, missed doses or had dose reductions due to adverse events. The most commonly reported events leading to missed doses and dose reductions in the VELCADE treatment group were peripheral neuropathy NEC, thrombocytopenia, neutropenia and diarrhea.

Adverse events leading to treatment discontinuation were reported in 37% of patients in the VELCADE treatment group and 29% of patients in the dexamethasone group. The most commonly reported treatment-emergent adverse event leading to discontinuation in the VELCADE group was peripheral neuropathy NEC (8%); all other events leading to discontinuation, including all events reported in the dexamethasone treatment group that led to discontinuation, occurred in 2% of patients or fewer.

Additional Phase II studies

See above *Patient Exposure*

Besides Phase III -039 Study, two Phase II studies provided data for the present safety update. These data are summarised below.

In study –025 41 (20%) patients experienced at least 1 treatment-emergent adverse event in the cardiac disorders SOC. At least 1 adverse event within this SOC was considered to be study drug-related for 6 (3%) patients and ≥Grade 3 in intensity for 13 (6%) patients. Adverse events of ≥Grade 3 intensity occurring within this SOC included congestive cardiac failure (5 patients; 2%), pulmonary edema (3 patients; 1%), tachycardia NOS (2 patients; <1%), and atrial fibrillation, cardiac amyloidosis, cardiac arrest, cardio-respiratory arrest, myocardial ischemia, and ventricular tachycardia (1 patient each; <1%). The incidence of Grade 4 adverse events within the cardiac disorders SOC was low (2%), with all Grade 4 adverse events reported within this SOC occurring at an incidence <1%. Overall, 5 (2%) patients experienced at least 1 adverse event of Grade 4 intensity within this SOC, including congestive cardiac failure (2 patients; <1%) and cardiac amyloidosis, cardiac arrest, cardio-respiratory arrest, and pulmonary edema (1 patient each; <1%).

In study –024 a total of 9 (17%) of the 54 patients experienced at least 1 treatment-emergent AE in the cardiac disorders SOC, including 5 (18%) patients in the 1.0 mg/m^2 dose group and 4 (15%) patients in the 1.3 mg/m^2 dose group. Cardiac disorders reported during the study included uncomplicated arrhythmias, rate abnormalities, arteriovenous (AV) block, or congenital abnormality. At least 1 AE within this SOC was considered to be study drug-related for 3 and 2 patients in the 1.0 and 1.3 mg/m^2 dose groups, respectively. All AEs occurring within this SOC were reported as Grade 1 or 2 in intensity; none were reported as serious. Two patients, both in the low dose group, discontinued study drug because of cardiac disorders; including Grade 2 supraventricular tachycardia considered probably related to study drug and Grade 1 ventricular extrasystoles considered possibly related to study.

Discussion on Clinical Safety

The rates of overall adverse events, Grade 4 adverse events, serious adverse events, and adverse events leading to discontinuation were similar between VELCADE and dexamethasone. The incidence of treatment-related deaths was low and similar in each treatment group (1% and 2%, respectively), and the incidence of treatment emergent deaths, irrespective of relationship to study drug, was lower on VELCADE (4%) than on dexamethasone (8%).

VELCADE was associated with peripheral sensory neuropathy. This neuropathy generally was Grade 1 or 2: the median time to improvement or resolution of ≥ Grade 2 peripheral neuropathy was ~3.5 months (107 days), and improvement or resolution was observed in about half of the patients.

VELCADE was associated with a very high incidence of gastrointestinal disorders, primarily reports of diarrhea, constipation, and nausea with or without vomiting. In general, these gastrointestinal disorders presented early during treatment, were Grade 1 or 2, and did not lead to a change in the dose or schedule of VELCADE.

A high rate of asthenic conditions (including fatigue, worsening of fatigue, malaise, lethargy, asthenia, and weakness) was also observed. Asthenic conditions generally presented early during treatment and

were Grade 1 or 2. The majority of patients who experienced asthenic condition continued VELCADE despite this event.

VELCADE was associated with thrombocytopenia and neutropenia; severe myelosuppression was uncommon. Typically, platelet and neutrophil counts recovered to baseline during the rest period between treatment cycles before initiation of each subsequent treatment cycle. Complications such as febrile neutropenia and significant bleeding events were uncommon, and the rates of such events in the phase 3 study were similar between VELCADE- and dexamethasone-treated patients.

Based on the data provided by the Applicant the bortezomib toxicity profile seems acceptable and within the usual range of cytotoxic therapies.

Benefit-risk assessment

The benefits of VELCADE treatment in patients with multiple myeloma who have had at least 1 prior therapy seems to outweigh the risks associated with this medicinal product with a predictable and relatively manageable safety profile. The data submitted from the Phase III study M34101-039 confirm the clinical benefit that was already suggested by the non-randomised Phase II studies that supported VELCADE approval in a refractory patient population, and provide evidence that it may be of benefit to a patient population earlier in the course of their disease.

A total of 669 patients were randomized to VELCADE or high-dose dexamethasone. Patients in both treatment groups had received a median of two prior lines of therapy, and 40% of patients in the VELCADE group and 35% of patients in the dexamethasone group had received only one prior line of therapy. Among those who had received only one prior line, 95% had received generally accepted, standard therapy that included an anthracycline and/or an alkylating agent. Based on stratification at randomization, 64% of patients were refractory to their last prior therapy.

VELCADE significantly improved overall and one-year survival compared to dexamethasone (hazard ratio 0.57, p=0.0013; hazard ratio 0.53, p=0.0005, respectively) despite the cross over of patients in the dexamethasone group who had progressive disease to receive VELCADE on the companion study M34101-040. The likelihood of survival at one-year was 80% on VELCADE and 66% on dexamethasone (p=0.0025). (RRR 41% in the first year on VELCADE treatment).

VELCADE significantly improved TTP (time to progression compared to dexamethasone (hazard ratio=0.55; p<0.0001). Median TTP was 189 days (6.2 months) for VELCADE and 106 days (3.5 months) for dexamethasone. This represents a 78% improvement in median TTP for VELCADE patients compared to dexamethasone patients.

VELCADE significantly improved overall response rate (CR + PR) (38% versus 18%, p<0.0001) and CR rate (6% versus <1%, p=0.0001) compared to dexamethasone. The proportion of patients who achieved CR or near CR (meeting all CR criteria except immunofixation positive) also was higher in the VELCADE group (13%) compared to the dexamethasone group (2%).

VELCADE responses were durable, with a median duration of response of 242 days (8.0 months) compared to 169 days (5.6 months) with dexamethasone. Responses to VELCADE and dexamethasone occurred rapidly, with a median time to first response (CR or PR) of 43 days. In those patients who achieved CR, the median time to first response was 23 and 24 days in the VELCADE and dexamethasone groups, respectively.

VELCADE also significantly improved survival, TTP and response rate in patients who were reported by the investigator to be refractory to their last prior therapy. In these 431 patients median TTP was 168 days (5.5 months) on VELCADE compared to 85 days (2.8 months) on dexamethasone (hazard ratio=0.49; p<0.0001); the hazard ratio for overall survival was 0.60 (p=0.0125), and overall response rate was 35% on VELCADE and 13% on dexamethasone (p<0.0001)

VELCADE also significantly improved survival, TTP and response rate in patients receiving second-line therapy on this study. In these 251 patients, who had received only one prior line of therapy, median TTP was 212 days (7.0 months) on VELCADE compared to 169 days (5.6 months) on dexamethasone (hazard ratio=0.56; p=0.0021); the hazard ratio for overall survival was 0.42 (p=0.0130), and overall response rate was 45% on VELCADE and 26% on dexamethasone (p=0.0035).

The possibility still stands that VELCADE is misunderstood as second line therapy in patients suitable to high-dose therapy (HCT) / stem cell transplantation (SCT). A total of 174/251 patients were suitable for HDT/SCT, 156 received HDT/SCT, 18 did not. The fact that 18 patients that could have received HDT/SCT, but did not, may unduly imply that VELCADE can be used as second line therapy in patients suitable to but not yet undergone transplantation. This is cause of concern as far as the relative efficacy of VELCADE and transplantation is not established and the possible deleterious effect of VELCADE on stem cells is not ruled out.

All of these efficacy measures occurred in the setting of a predictable and manageable safety profile that was similar to the safety profile seen in the Phase II studies. The rates of grade 4 adverse events, discontinuations due to adverse events, serious adverse events and treatment-related mortality were all similar between VELCADE, and dexamethasone, a non-cytotoxic agent. Study M34101-039 also confirms VELCADE activity in patients who were reported to be refractory to last prior therapy.
Toxicities associated with VELCADE were generally reversible. Serious toxicity (≥Grade 3) was manifest primarily by transient uncomplicated thrombocytopenia, fatigue, and peripheral neuropathy. In addition, the safety profile was similar in the 63 patients who received prolonged therapy with VELCADE on the extension study M34101-029, and no new safety risks have been identified.

In light of this favourable benefit/risk profile and the clarifications provided by the MAH, VELCADE may be recommended for use in patients with myeloma after documented failure of at least one prior therapy. However, there is still some concern with regard to the fact that comparison of VELCADE was limited to dexamethazone though other options of proven efficacy were available and to the possiblity that VELCADE can be perceived as an alternative to bone marrow transplantation and other effective therapeutic options. Therefore, the following wording of SPC section 4.1 was agreed by the CHMP:

"VELCADE is indicated as mono-therapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation."