European Medicines Agency

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ASSESSMENT REPORT FOR VELCADE

International non-proprietary name/Common name: bortezomib

Procedure No. EMEA/H/C/000539/II/0028

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

Velcade (bortezomib) is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in orchestrating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.

On 26 April 2004, Velcade was authorised under exceptional circumstances in the European Union where it is currently indicated in 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.

In the present application, the Marketing Authorisation Holder (MAH) of Velcade applied for an extension of indication for the treatment of patients with previously untreated multiple myeloma with subsequent changes in sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the Summary of Product Characteristics. The Package Leaflet is proposed to be updated accordingly.

The following indication in section 4.1 has been agreed:
"Velcade in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant."

2. Clinical aspects

Velcade for injection is currently approved in 85 countries for the treatment of relapsed multiple myeloma in patients who have progressed after receiving at least 1 previous line of treatment. It was granted a marketing authorisation in the European Union in 2004 initially as therapy in patients with multiple myeloma who had received at least 2 prior lines of treatment. Subsequently, the indication was extended to treat patients with multiple myeloma earlier in the course of the disease (EMEA/H/C/539/II/05, Commission Decision on 20 April 2005).

Multiple myeloma (also known as myeloma or plasma cell myeloma, MM) is a progressive hematologic disease. It is characterized by excessive numbers of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulin (IgG, IgA, IgD, or IgE) or Bence-Jones protein (free monoclonal κ and λ light chains). The estimated incidence of MM in Europe is 23,000 per year. MM is still considered to be an incurable disease and the 5-year relative survival rate is around 33%. Median age at diagnosis is 65 to 70 years, with the incidence of myeloma increasing with age. Multiple myeloma usually manifests as 1 or more lytic bone lesions, monoclonal protein in the blood or urine, and disease in the bone marrow. Disease progression is often associated with worsening of symptoms and organ dysfunction characteristic of myeloma, such as anemia, bone lesion-related symptoms, renal function impairment, and susceptibility to infections. Current treatment options, therefore, aim not only to improve survival but also to induce tumour response, inhibit tumour progression, and delay disease-related complications.

The current recommendation is to incorporate high-dose chemotherapy with stem cell transplant (HDT/SCT) into initial therapy programs for patients 65 years of age or younger. In patients older than 65 years of age, the value of HDT/SCT is controversial and has not been formally established even in prospective randomized studies. Given that the median age at diagnosis of multiple myeloma is between 65 and 70 years, the majority of newly diagnosed patients is treated only with standard chemotherapy, with no consideration for HDT/SCT because of poor physical condition, co-morbidities, and increased toxicity.

Standard chemotherapy regimens include melphalan-prednisone (MP), VAD (vincristine-doxorubicin-dexamethasone), thalidomide-dexamethasone, and alkylating-agent combinations. Combination

chemotherapy with MP has been the standard-of-care in front-line non-transplant multiple myeloma therapy since the 1960s, and remains the most widely accepted treatment option for patients ineligible for HDT/SCT.

The present application is supported by Study MMY-3002, designed to determine whether the addition of Velcade to standard MP therapy (Vc-MP) would improve the outcome of previously untreated patients with multiple myeloma.

2.1 Clinical pharmacology

As a sub-study of the Phase 3 Study MMY-3002, the pharmacokinetics (PK) of Velcade with and without co-administration of MP was examined during the first 2 cycles of treatment with Velcade. Twenty-seven (27) subjects were enrolled into this study in 6 countries but only 20 of them completed the sub-study.

The PK parameters of Velcade administered alone or in combination with melphalan and prednisone are presented in the tables below.

Table 1 – Mean (SD) VELCADE Pharmacokinetic Parameters in Subjects Following i.v. Administration of VELCADE (1.3 mg/m^2) With and Without Melphalan and Prednisone (Study MMY-3002-PK: Subjects Evaluable for Pharmacokinetics)

PK Parameter	VELCADE Alone (n=20)	Vc-MP (n=20)
t_{max} (h) [a]	0.08 (0.08-0.50)	0.08 (0.08-1.00)
C_{max} (ng/mL)	207 (505)	165 (300)
AUC_{24h} (ng•h/mL)	88.4 (62.7)	108 (76.2)
AUC_{∞} (ng•h/mL)	126 (65.1)	148 (77.1)
CL (L/h)	20.3 (6.29)	18.2 (7.84)
V_Z (L)	541 (156)	469 (202)
$t_{1/2}$ (h)	18.9 (4.1)	18.3 (4.5)
λ_z (h^{-1})	0.0381 (0.00708)	0.0401 (0.00947)

[a] Data presented as median (min-max)

Table 2 - Results of Geometric Mean Ratios and 90% Confidence Intervals of the PK Parameters of VELCADE Alone or in Combination with Melphalan and Prednisone (Vc-MP)

PK Parameter	%CV	N	Geometric Mean		Ratio	90% Confidence Interval		P value
			VELCADE	Vc-MP		Lower	Upper	
AUC_{24h} (ng*h/mL)	40.6	20	78.795	92.882	1.179	0.944	1.472	0.2154
AUC_{∞} (ng*h/mL)	35.7	20	116.004	133.818	1.154	0.949	1.402	0.2207
C_{max} (ng/mL)	69.1	20	95.450	86.720	0.909	0.623	1.326	0.6657

Overall, the pharmacokinetic profile of Velcade in this study was similar to that previously reported. All pharmacokinetic parameter values were comparable between the two groups, although inter-individual variability was high when Velcade was given alone or in combination with MP. The large apparent volume of distribution of Velcade suggested extensive peripheral tissue distribution, which was similar for all study days and treatments. Due to the high degree of inter-subject variability, the 90% confidence intervals of mean plasma peak concentration and exposure measures extended beyond the regulatory guideline range of 80% to 125%. However, a closer interpretation of individual profiles and graphical data analysis indicated that there was no apparent drug-drug interaction when MP was co-administered with Velcade. This interpretation is supported by the clinical data in Study MMY-3002, indicating a similar dose intensity of melphalan in the Velcade + MP (Vc-MP) and MP treatment groups, and a dose intensity of Velcade in the Vc-MP treatment group is consistent with prior single-agent Velcade studies. Therefore, a statement is included in section 4.5 to reflect that the 17% increase in mean bortezomib AUC observed was not considered as clinically relevant.

2.2 Clinical efficacy

- Methods

Study design

Study MMY-3002 was a randomized, open-label, multicenter study to compare the efficacy and safety of Velcade plus standard MP therapy versus MP therapy in subjects with previously untreated multiple myeloma who were not considered candidates for HDT/SCT.

The study consisted of 3 Phases: a pre-randomization (screening) phase, an open-label treatment phase, and a post-treatment follow-up phase. In the post-treatment follow-up phase, subjects were followed until death or a maximum of 4.5 years after the last subject was randomized in the study.

Study population

The study population included men and women with previously untreated symptomatic multiple myeloma or asymptomatic multiple myeloma with related organ or tissue damage who were not candidates for HDT/SCT due to age (65 years or older) or, in subjects less than 65, presence of important comorbid condition(s) likely to have a negative impact on the tolerability of HDT/SCT. Presence of measurable disease was required for both secretory multiple myeloma and for oligosecretory or nonsecretory multiple myeloma.

In order to ensure that the treatment arms were well balanced and unbiased, randomization, with a 1:1 allocation ratio, was stratified by baseline beta$_2$-microglobulin and baseline albumin (both independent prognostic factors in untreated multiple myeloma), as well as by region (North America, Europe, other).

Dose and Schedule

A 6-week treatment cycle for Vc-MP and MP was selected to align the Velcade treatment regimen with the MP treatment regimen used in many studies in past, and to provide consistency and to ensure continued symmetry in efficacy and safety assessments across treatment.

Treatment for newly diagnosed multiple myeloma is often continued for a fixed time period of 6 to 12 months or until a response plateau is reached. A 12-month (54-week) duration of therapy (the same for both treatment arms) was chosen on the basis of historical data on the average duration of MP therapy and the lack of benefit of maintenance therapy with MP, as well as the prescribing information for melphalan. A fixed duration of therapy was chosen for Study MMY-3002 to minimize the potential impact of heterogeneity in geographic treatment patterns on the time-dependent primary endpoint.

In Study MMY-3002, melphalan was dosed at 9 mg/m^2 (approximately equivalent to the 0.25 mg/kg dose originally used), together with the most frequently used steroid regimen of prednisone, 60 mg/m^2 per day on Days 1 to 4 of each 6-week cycle.

In the Vc-MP treatment group, Velcade was added to MP for the entire 54-week duration of treatment at a dose of 1.3 mg/m^2. During the first 24 weeks, Velcade was given twice weekly for 2 consecutive weeks, followed by a week off. In order to match the 6-week MP cycle, 2 of these 3-week treatment periods were considered 1 cycle of Velcade. This dose and twice-weekly cycle is the same as currently approved for patients with previously treated multiple myeloma. After 24 weeks, a less dose-intense, i.e., weekly regimen, of Velcade was administered.

Endpoints

The primary endpoint was Time to Progression (TTP). Secondary endpoints included Progression-Free Survival (PFS), Overall Survival (OS), Overall Response (OR) rate, Complete Response (CR) rate, time to first response, duration of response, and patient-reported outcomes.

Efficacy assessments included the following: myeloma protein (M-protein) measurements in serum and 24-hour urine including immunofixation testing, bone marrow examination, skeletal survey, documentation of extramedullary plasmacytomas, and serum calcium level adjusted for albumin.

To assess other potential indications of clinical benefit, additional analyses included the effects of Vc-MP and MP on: time to subsequent therapy; myeloma-related complications (incidence of hypercalcemia, incidence of renal function impairment, incidence of anemia, incidence of skeletal events); Grade 3 or 4 infection rates; and immune reconstitution of normal immunoglobulins.

- Results

Study population

At the time of the clinical cut-off date of 15 June 2007 for the third interim analysis, 682 subjects from 151 centers in 22 countries were enrolled into Study MMY-3002, with 344 subjects randomized to the Vc-MP treatment group and 338 subjects randomized to the MP treatment group. Of the 682 randomized subjects (intent-to-treat [ITT] population), 677 were treated (safety population), with 668 of these subjects further included in the response-evaluable population. On 15 June 2007, 45% of Vc-MP subjects and 41% of MP subjects had completed all 9 cycles of study treatment, while 14% and 10%, respectively, were still undergoing treatment. Demographics, baseline disease characteristics, and extent of disease at baseline were well balanced between the 2 treatment groups. Treatment groups were distributed similarly by region, with the majority (79%) of subjects enrolled at sites in the Europe/Australia Region. The patient population was mainly (80%) Caucasian.

Table 3 provides a summary of selected baseline and disease characteristics for the Vc-MP and MP treatment groups in Study MMY-3002.

Table 3 - Summary of Baseline Subject and Disease Characteristics (Study MMY-3002)

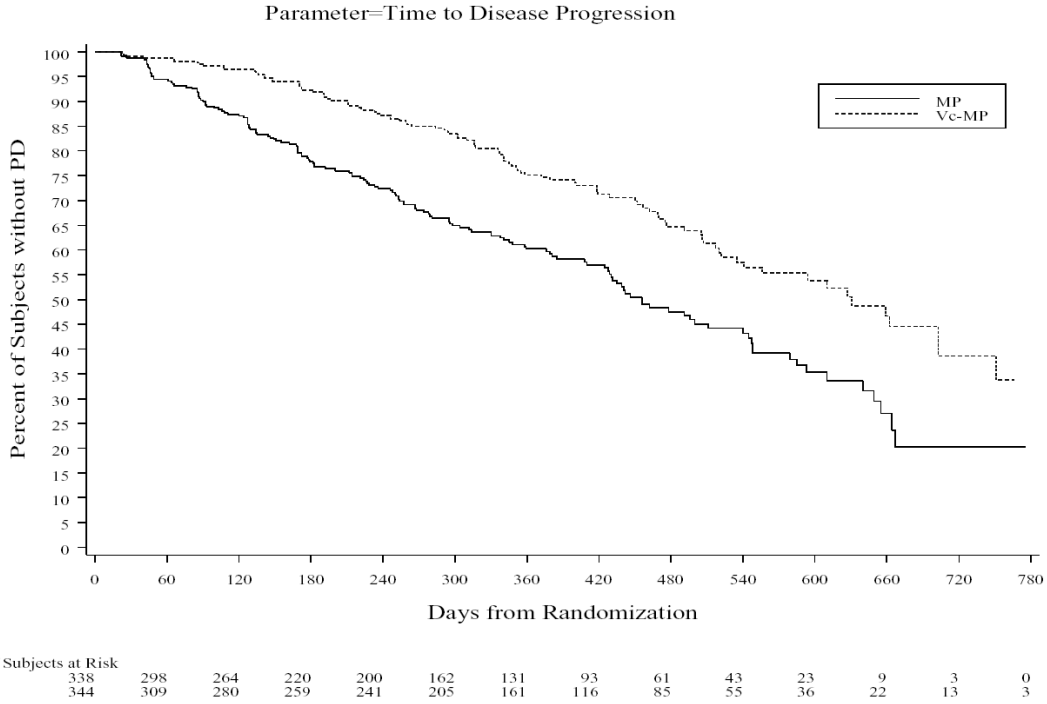
	Vc-MP (N=344)	MP (N=338)	Total (N=682)
Subject Characteristics			
Median age in years (range)	71.0 (57, 90)	71.0 (48, 91)	71.0 (48, 91)
Gender: male/female (%)	51/49	49/51	50/50
Race: White/Asian/Black/Other (%)	88/10/1/1	87/11/2/0	88/10/2/<1
Karnofsky Performance Status Score ≤70	35%	33%	34%
Hemoglobin <100 g/L	37%	36%	36%
Platelet count <75 x 10^9/L	<1%	1%	1%
Disease Characteristics			
Type of myeloma (%): IgG/IgA/Light chain	64%/24%/8%	62%/26%/8%	63%/25%/8%
Median beta$_2$-microglobulin (mg/L)	4.2	4.3	4.3
Median albumin (g/L)	33.0	33.0	33.0
Creatinine clearance ≤30 mL/min (n [%])	20 (6%)	16 (5%)	36 (5%)
ISS Stage I/II/III (%)	19/47/35	19/47/34	19/47/34

Vc-MP=VELCADE-melphalan-prednisone; MP=melphalan-prednisone

Primary Efficacy Endpoint: Time to Progression

There was a statistically significant difference in TTP, the primary efficacy endpoint, in favour of subjects treated with Vc-MP. The median TTP was 20.7 months (631 days) in the Vc-MP treatment group compared with 15.0 months (456 days) in the MP treatment group (hazard ratio=0.540; p=0.000002), demonstrating a 46% decrease in the risk of progression/relapse for subjects in the Vc-MP group (Figure 1).

Figure 1 - Time to Disease Progression (Study MMY-3002: All Randomized Subjects Analysis Set)

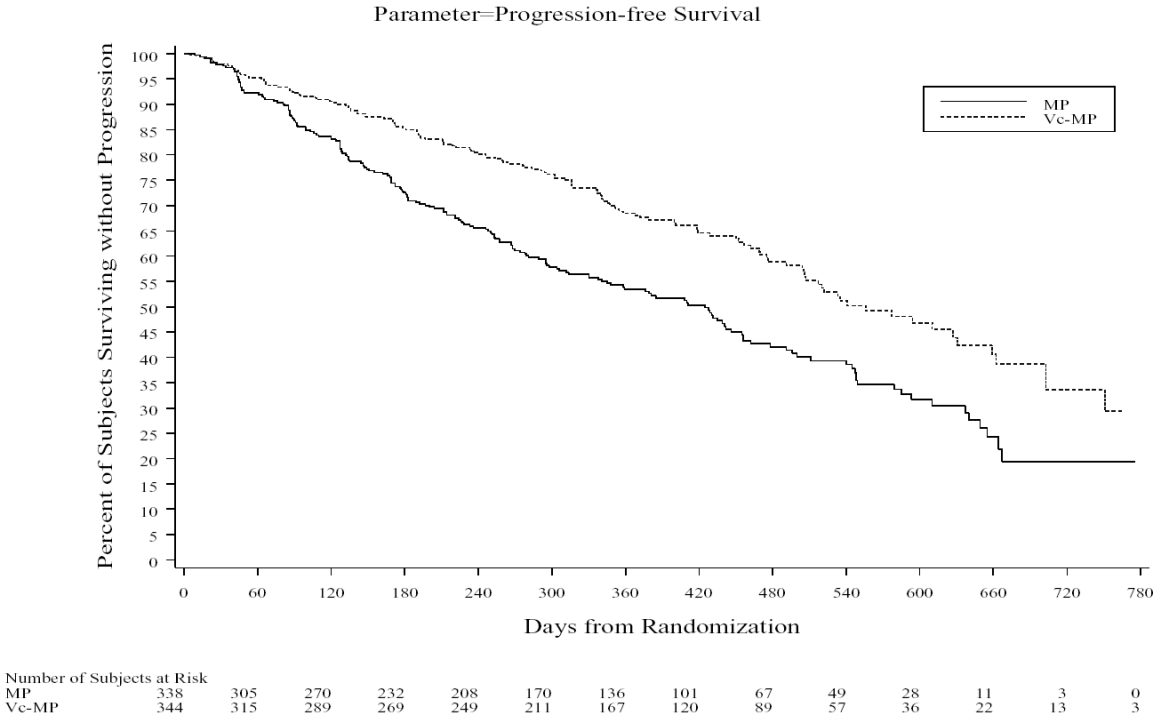


Several sensitivity analyses, including TTP as determined by the investigator and TTP (as determined by algorithm) without censoring for subsequent therapies, were performed and were consistent with the conclusions from the primary analysis.

Secondary Efficacy Endpoint: Progression-Free Survival

The difference in PFS in favour of Vc-MP-treated subjects was statistically significant and consistent with the results of the TTP analysis. Median PFS was 18.3 months (556 days) in the Vc-MP treatment group and 14 months (425 days) in the MP treatment group (hazard ratio=0.609; p=0.00001) (Figure 2).

Figure 2 - Progression-Free Survival (Study MMY-3002: All Randomized Subjects Analysis Set)



Number of Subjects at Risk

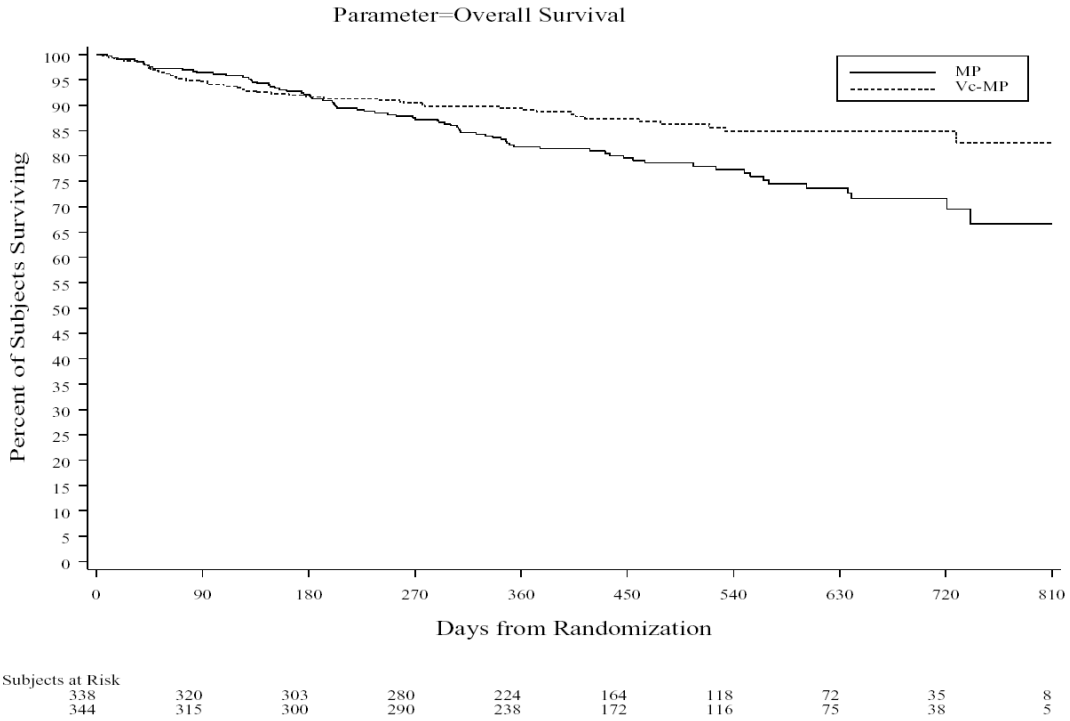
MP	338	305	270	232	208	170	136	101	67	49	28	11	3	0
Vc-MP	344	315	289	269	249	211	167	120	89	57	36	22	13	3

Secondary Efficacy Endpoint: Overall Survival

A significant survival benefit favouring the Vc-MP treatment group was demonstrated (hazard ratio=0.607; p=0.00782). At the time of the clinical cut-off, representing a median follow-up of 16.3 months, 121 subjects had died (45 subjects [13%] in the Vc-MP treatment group and 76 subjects [23%] in the MP treatment group) (Figure 3). While median OS was not reached in either treatment group, the 1-year survival rate in the Vc-MP and MP treatment groups was 89.1% and 81.8%, respectively. The 2-year survival rate in the Vc-MP and MP treatment groups was 82.6% and 69.5%, respectively.

Sixty-eight subjects (20%) in the Vc-MP treatment group and 121 subjects (36%) in the MP treatment group received subsequent therapy by the time of the clinical cut-off for the third interim analysis. In the Vc-MP treatment group, 8 of the 68 subjects (12%) received subsequent therapy with Velcade, while 54 of the 121 subjects (45%) in the MP treatment group received subsequent therapy with Velcade.

Figure 3 - Overall Survival (Study MMY-3002: All Randomized Subjects Analysis Set)



Secondary Efficacy Endpoint: Best Response to Treatment

The improvement in TTP observed in the study was supported by statistically significant differences in favour of subjects in the Vc-MP treatment group in OR and CR rates. The OR rate (CR+PR) was 71% in the Vc-MP treatment group and 35% in the MP treatment group (odds ratio=4.5; p<10-10). One hundred and two subjects (30%) in the Vc-MP treatment group and 12 subjects (4%) in the MP treatment group had a CR (odds ratio=11.2;p<10-10). Partial response was reported in 136 subjects (40%) in the Vc-MP treatment group and 103 subjects (31%) in the MP treatment group. Five subjects in the Vc-MP treatment group had an immunofixation-positive CR (IF+ CR).

Secondary Efficacy Endpoint: Time to First Response

For those subjects who responded to treatment, median time to first response was 1.4 months (43 days) in the Vc-MP treatment group and 4.2 months (128 days) in the MP treatment group. The median time to best response and median time to CR was 2.3 months (69 days) and 4.2 months (127 days), respectively, in the Vc-MP treatment group and 4.9 months (148 days) and 5.3 months (161 days) in the MP treatment group, respectively.

For all subjects, based on Kaplan-Meier estimates, time to first response (hazard ratio=3.874; p<10-10), time to best response (hazard ratio=3.155; p<10-10), and time to CR (hazard ratio=9.152; p<10-10) were significantly earlier in Vc-MP-treated subjects compared with MP-treated subjects.

Although most responses occurred early, there were, however, some late de novo responses in the Vc-MP treatment group which, according to the applicant, justified the use of 54 weeks schedule. In particular, 9 PRs (9/228 subjects [4%]) occurred after the initial 24 weeks and during the weekly treatment Cycles 5 to 9. Moreover, response for subjects receiving Vc-MP continued to improve with continuing therapy. Twenty-nine of 102 CRs (28%) in the Vc-MP treatment group obtained a CR as their best response after the first 24 weeks of treatment (converted from PR on the twice-weekly treatment cycles [Cycles 1 to 4] to CR on the weekly treatment [Cycles 5 to 9]). This can be seen as a justification to continue the therapy for the protocol-defined treatment period (i.e., 54 weeks). Since CR is reported to be associated with prolonged TTP and survival, these data suggest that continued therapy results in clinical benefit. The number of patients gaining benefit from the longer treatment are, however, not very high.

Secondary Efficacy Endpoint: Duration of Response

Tumour responses obtained on the Vc-MP regimen were durable. The median duration of response, by the Kaplan-Meier method, was 19.9 months (606 days) in the Vc-MP treatment group and 13.1 months (400 days) in the MP treatment group.

An analysis of the duration of response by best response category (CR or PR) also was performed. The median duration of response for subjects whose best response was a CR was 24 months (729 days) in the Vc-MP treatment group and 12.8 months (389 days) in the MP treatment group. For subjects whose best response was a PR, the median duration of response was 15.2 months (464 days) and 13.1 months (400 days), respectively.

To understand the effect of duration of Vc-MP treatment on the duration of CR, an analysis was performed of the duration of CR by the number of additional cycles received beyond the first documentation of CR. The median duration of CR was 16.9 months (513 days) for subjects who received ≤2 additional cycles after CR and 20.3 months (617 days) for subjects with CR who completed 9 cycles of treatment. This analysis indicates that continuation of treatment results in prolonged duration of CR.

Secondary Efficacy Endpoint: M-Protein Response

M-protein is accepted as a valid measure of tumour burden and consequently of tumour response and progression. Change in M-protein values is the most important component of response and progression assessments in multiple myeloma. To facilitate comparisons between data from Study MMY-3002 and historical data using best M-protein response as the basis for response assessment, an analysis of best M-protein response was performed. Thirty-seven percent of subjects in the Vc-MP treatment group and 7% of subjects in the MP treatment group had 100% reduction of M-protein in the serum or urine at some point during the study. Forty-five percent and 10% of subjects in the Vc-MP and MP treatment groups, respectively, had a ≥90% reduction (consistent with VGPR in historical studies) and 82% and 50% of subjects in the Vc-MP and MP treatment groups, respectively, had a ≥50% reduction in M-protein.

Secondary Efficacy Endpoint: Time to Subsequent Myeloma Therapy

Time to subsequent myeloma therapy was significantly longer for subjects in the Vc-MP treatment group compared with the MP treatment group. Of the 682 randomized subjects, 73 subjects (21%) and 127 subjects (38%) in the Vc-MP and MP treatment groups, respectively, received subsequent therapy as of the clinical cut-off date of 15 June 2007. The median time to subsequent myeloma therapy, measured from randomization, was 20.8 months (632 days) in the MP treatment group and had not been reached in the Vc-MP group (hazard ratio=0.522; p=0.000009). Five of 8 subjects in the Vc-MP treatment group who were retreated with Velcade had an investigator-reported response assessment; of these 5 subjects; 1 obtained a CR and 2 obtained a PR. Thirty-six of 54 subjects in the MP treatment group who were subsequently treated with Velcade had an investigator-reported response assessment; of these 36 subjects, 5 obtained CR and 16 obtained PR.

Subgroup analyses

The following subgroup analyses were performed relative to the primary efficacy endpoint, TTP, as well as several secondary efficacy parameters (PFS, OS, OR):

- Baseline stratification factors: beta2-microglobulin, albumin, and region.
- Demographic data: gender, race, and age.
- Baseline disease characteristics: ISS staging and cytogenetic risk.

Baseline demographics and disease characteristics were comparable across both treatment groups. A substantial proportion of subjects in both groups entered the study with adverse prognostic features including age ≥75 years (30%); KPS score ≤70 (34%), beta2-microglobulin >5.5 mg/L (33%); albumin <3.5 g/dL (60%); and ISS Stage III disease (34%).

A treatment effect was demonstrated in the Vc-MP treatment group, compared with the MP treatment group for the primary and all secondary efficacy endpoints across all subgroups evaluated (hazard ratios <1 or odds ratio >1). The OR rates and CR rates on Vc-MP were similar across subgroups, including subgroups with these indicators of poor prognosis. In particular, high CR rates and OR rates were observed within the Vc-MP treatment group in the beta2-microglobulin >5.5 mg/L subgroup (49% and 71%, respectively), Stage III subgroup (37% and 72%, respectively), and high-risk cytogenetic subgroup (29% and 68%, respectively), demonstrating consistent activity of Velcade in subjects with previously untreated multiple myeloma with the worst prognostic factors.

Additional analyses

Based on Study MMY-3002, the proposed duration of treatment in patients with previously untreated multiple myeloma is 54 weeks (nine 6-week cycles). The normal duration of MP-treatment is either 6 or 12 months. The currently approved duration of treatment with Velcade is however of 24 weeks. At the request from the CHMP, the MAH provided additional analyses of the results after both 24 and 54 weeks, in order to justify a longer treatment duration.

Twenty-nine (29) patients out of 102 (28%) obtained a CR or a first response only after 24 weeks. Nine additional subjects obtained their first response (partial response [PR]) also after the first 24 weeks. Obtaining a CR is indicative of a prolonged duration of response (median 24 months for CR as compared with 15.2 months for PR) and is associated with a prolonged time to progression and overall survival.

To further substantiate the long-term benefit obtained by these late responders, the MAH provided an analysis of TTP and survival in the 29 Vc-MP subjects who obtained CR after 24 weeks of treatment as compared with subjects who obtained CR within 24 weeks. The subjects who obtained these later CRs had a numerically better time to progression (median not reached vs. 21.7 months) and better 2-year survival (96.6% vs. 90.6%) compared with subjects who obtained CRs earlier. Similarly, the 9 subjects who obtained a PR after 24 weeks of treatment had a numerically better time to progression (median 23.1 vs. 17.1 months) and better 2-year survival (100% vs. 83.6%) compared with subjects who obtained PRs earlier.

The MAH also provided an analysis of time-to-event outcomes of subjects in the Vc-MP treatment group whose duration of Velcade treatment was ≤4 cycles (24 weeks) as compared to those with a duration of Velcade treatment >4 cycles. Median TTP was 18.3 months and 20.7 months, respectively; median PFS was 12.1 months and 20.7 months, respectively; 2-year survival was 73% and 88.7%, respectively. OS was not reached in either treatment group. However, the study was not optimally randomized to perform a comparison of efficacy results at ≤4 cycles and >4 cycles. This may lead to a distortion of the results as those who failed already in the beginning impair the results in the first group.

- Discussion on clinical efficacy

In Study MMY-3002, statistically significant improvement of TTP was observed with Vc-MP treatment compared to MP only treatment in patients with previously untreated multiple myeloma. Consistent statistically significant results were observed on the secondary endpoints including PFS and OS. Treatment effect was maintained across all subgroups tested. Additionally, responding subjects in the Vc-MP group experienced substantially longer duration of response relative to the MP subjects. In addition, the time to subsequent therapy was extended and there was also an improvement in myeloma-related complications. These results are supportive of the clinical superiority of Vc-MP treatment compared to MP treatment and can be reflected in section 5.1 of the SPC.

The CHMP Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev. 3/Corr. 2) indicates that acceptable endpoints for confirmatory trial include OS and PFS/DFS. If PFS/DFS is the selected primary endpoint, OS should be reported as a secondary

and vice versa. Alternative primary endpoints, such as TTP, TTF or EFS might uncommonly be appropriate.

At the request from the CHMP, the MAH provided further justifications on the use of TTP as a primary endpoint in Study MMY-3002. The MAH considered that TTP and PFS are both considered measures of clinical benefit in multiple myeloma, since these endpoints mark progression and worsening of disease that is inevitably fatal. TTP directly measures tumour growth over time in all patients. However, PFS includes deaths due to toxicity as well as other causes, which makes the interpretation of treatment effect more complex. Particularly in this elderly patient population with many co-morbidities, it was expected that there would be a substantial number of deaths due to causes unrelated to cancer, which would confound the treatment effect on PFS. Since a change in therapy is often triggered by progression, TTP is not confounded by subsequent therapies or cross-over unlike OS. Although TTP was chosen as the primary endpoint, PFS analysis was considered to be a very important endpoint and was included as a secondary endpoint in the study objectives. PFS analysis was considered to be a critical sensitivity analysis for TTP. A compelling outcome based on TTP would enable a much needed advance for newly diagnosed multiple myeloma patients to become available years and months before a conclusive result would be available based on survival data. The CHMP considered the justification provided by MAH on the choice of TTP as primary endpoint to be acceptable.

As some patients did receive the response only after 24 weeks and as the adverse events during those last 30 weeks do not seem to increase, 54 weeks of treatment can be considered as giving an additional benefit to 24 weeks treatment. Therefore, the CHMP considered the proposed duration of 54 weeks of treatment to be acceptable for inclusion in section 4.2 Posology and Method of Administration of the SPC.

2.3 Clinical safety

- Patient exposure

Of the 682 subjects randomized into Study MMY-3002, 677 subjects received at least 1 dose of study medication and are included in the safety population (340 treated with Vc-MP combination therapy and 337 treated with MP therapy). In addition, the safety data from the Vc-MP treatment group in Study MMY-3002 were compared with integrated safety data from 5 previous studies of single-agent Velcade, used at the approved dose of 1.3 mg/m^2, in subjects with previously treated multiple myeloma. The 5 studies included Studies M34100-024 (26 subjects), M34100-025 (202 subjects), M34101-039 (331 subjects), M34101-040 (449 subjects), and JPN-MM-101 (25 subjects). A combined total of 1,033 subjects with multiple myeloma received single-agent Velcade in these studies.

- Adverse events

The incidence of treatment-emergent adverse events is summarized in Table 4 for the Vc-MP and MP treatment groups in Study MMY-3002, as well as for single-agent Velcade used in prior studies. As exposure was longer in Study MMY-3002 than in prior studies in relapsed subjects, the incidence of adverse events was adjusted for length of exposure.

Table 4 – Overview Summary of Treatment-Emergent Adverse Events (Multiple Myeloma SCS)

	Previously Untreated				Previously Treated	
	Vc-MP (N=340)		MP (N=337)		VELCADE (N=1033)	
Description	Unadjusted, N (%)	Exposure-Adjusted[a]	Unadjusted, N (%)	Exposure-adjusted[a]	Unadjusted, N (%)[d]	Exposure-adjusted[a]
Any TEAE	338 (99)	2.2472	326 (97)	0.9310	1031 (>99)	4.6573
At least one Related[b]	331 (97)	1.2636	283 (84)	0.3255	1002 (97)	2.2450
At least one VELCADE-related	331 (97)	1.1354			1002 (97)	2.2450
Any Serious TEAE	155 (46)	0.0655	121 (36)	0.0477	541 (52)	0.1307
Grade 1	2 (1)	0.0006	12 (4)	0.0040	16 (2)	0.0027
Grade 2	32 (9)	0.0104	47 (14)	0.0170	174 (17)	0.0335
Grade 3	181 (53)	0.0901	148 (44)	0.0630	615 (60)	0.1708
Grade 4	96 (28)	0.0365	92 (27)	0.0351	225 (22)	0.0414
Grade 5	27 (8)	0.0082	27 (8)	0.0088	1 (<1)	0.0002
Grade≥3	304 (89)	0.2268	267 (79)	0.1398	841 (81)	0.2677
Terminated Treatment Due to AEs[c]	50 (15)	0.0076	47 (14)	0.0077	356 (34)	0.0650
At least one related[b]	37 (11)	0.0056	35 (10)	0.0057	236 (23)	0.0423
At least one VELCADE-related	33 (10)	0.0050	NA	NA	236 (23)	0.0423
Discontinued VELCADE Due to AEs	108 (32)	0.0379	NA	NA	356 (34)	0.0650

Vc-MP=VELCADE-melphalan-prednisone; MP=melphalan-prednisone; TEAE=treatment emergent adverse event; AE=adverse event

[a] Exposure-adjusted incidence rate equals the number of subjects with events divided by the sum of time to first event (in patient-months).

[b] For Study MMY-3002, it includes all adverse events that were related to 1 of the 3 study drugs: VELCADE, melphalan, or prednisone.

[c] For Study MMY-3002, it includes those subjects indicated as having discontinued treatment due to an adverse event on the treatment termination case report form page.

[d] In the VELCADE group, Grade 5 is only available in the JPN-MM-101 study (total N for JPN-MM-101 is 25).

In Study MMY-3002, nearly all subjects in both treatment groups were reported to have at least 1 treatment-emergent adverse event. The incidence rate was higher in the Vc-MP treatment group than the MP treatment group for Grade 3 adverse events (53% vs. 44%) and serious adverse events (46% vs. 36%). However, the incidences were similar for Grade 4 adverse events (28% vs. 27%), Grade 5 adverse events (8% for both), and adverse events leading to treatment termination (15% vs. 14%).

Comparison of the Vc-MP and single-agent Velcade groups revealed a similar incidence of Velcade-related events (97% for both) and serious adverse events (46% vs. 52%) (Table 4). However, when analyzed by length of exposure, the incidence rates (per patient-months) appeared to be lower for Vc-MP than for single-agent Velcade for these 2 types of events. Exposure-adjusted incidence rates for the Vc-MP and single-agent Velcade treatment groups were 1.1354 vs. 2.2450 events per patient-month for Velcade related adverse events, and 0.0655 and 0.1307 events per patient-month for serious adverse events.

The incidence of Grade ≥3 adverse events was 89% for Vc-MP and 81% for single-agent Velcade. The exposure-adjusted incidence rate of Grade ≥3 events appeared to be lower for Vc-MP than for single-agent Velcade (0.2268 vs. 0.2677 events per patient-month). The incidence of termination of all study treatment because of adverse events was 15% for the Vc-MP treatment group and 34% for the single-agent Velcade treatment group, corresponding to exposure-adjusted incidence rates of 0.0076 and 0.0650 events per patient-month, respectively. The incidence of adverse events leading to Velcade discontinuation was similar with Vc-MP treatment (32%) and single-agent Velcade (34%). The exposure-adjusted incidence rate again appeared to be lower for Vc-MP than for single-agent Velcade (0.0379 vs. 0.0650 events per patient-month, respectively).

In conclusion, for all adverse event groups summarized in Table 4, the exposure-adjusted incidence rates were similar (and for several groups even lower) for the Vc-MP treatment group as compared with the single-agent Velcade treatment group.

The incidences of treatment-emergent adverse events were also examined by cycle for the Vc-MP group versus the MP group (Table 5). In the Vc-MP group, the incidence of treatment-emergent adverse events was higher with twice-weekly Velcade dosing during Cycles 1 to 4 (99%) compared

with weekly Velcade dosing during Cycles 5 to 9 (90%). A similar trend was seen in the MP treatment group (95% during Cycles 1-4 and 88% during Cycles 5-9). Additionally, within the first 4 cycles, the incidence of adverse events was higher during Cycles 1 to 2 compared with Cycles 3 to 4 in both the Vc-MP treatment group (98% and 93%, respectively) and the MP treatment group (90% and 84%).

The Vc-MP treatment group also had a higher incidence of Grade ≥3 (85%) and serious (40%) treatment-emergent adverse events during the first 4 cycles (twice-weekly regimen) compared with the MP treatment group (66% and 29%, respectively). However, a decreased incidence of Grade ≥3 (57%) and serious treatment-emergent adverse events (12%) was seen over time in the Vc-MP treatment group during Cycles 5 to 9 (weekly regimen) compared with Cycles 1 to 4 (twice-weekly regimen). This incidence of Grade ≥3 and serious adverse events in the Vc-MP treatment group (57% and 12%, respectively) was similar to that seen in the MP treatment group (61% and 15%, respectively) for the weekly Cycles 5 to 9. Also, the incidence of new all-grade adverse events was similar (88% and 90%, respectively) in the Vc-MP and MP treatment groups during weekly Cycles 5 to 9, suggesting that there is no cumulative toxicity with the addition of Velcade to MP.

Table 5 – Overview of Treatment-Emergent Adverse Events by Cycle: New Onsets (Study MMY-3002: Safety Analysis Set)

	MP					Vc-MP				
	Total	Cycle, n (%)				Total	Cycle, n (%)			
	(N=337)	1-2	3-4	1-4	5-9	(N=340)	1-2	3-4	1-4	5-9
Parameter	n (%)	(N=337)	(N=289)	(N=337)	(N=234)	n (%)	(N=340)	(N=284)	(N=340)	(N=249)
Any TEAE	326 (97)	302 (90)	244 (84)	319 (95)	207 (88)	338 (99)	332 (98)	265 (93)	338 (99)	224 (90)
Any Grade ≥3 TEAE	267 (79)	189 (56)	128 (44)	221 (66)	143 (61)	304 (89)	255 (75)	170 (60)	288 (85)	142 (57)
Any Serious TEAE	121 (36)	68 (20)	39 (13)	97 (29)	36 (15)	155 (46)	109 (32)	40 (14)	137 (40)	31 (12)
Treatment Termination Due to AEs*	47 (14)	17 (5)	11 (4)	28 (8)	15 (6)	50 (15)	29 (9)	14 (5)	40 (12)	11 (4)

MP=melphalan-prednisone; Vc-MP=VELCADE-melphalan-prednisone; TEAE=treatment emergent adverse event; AE=adverse event
Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Percentages of cycle sub-groups calculated with number of subjects per sub-group as denominator.
Note: A subject is counted only once within a particular cycle category, but may be counted more than once across categories.
A subject is counted as having an event within a particular cycle if a new onset of the event occurred within the cycle.
*The cycle reported is the cycle in which the onset of the AE(s) occurs.

Table 6 summarizes the most common treatment-emergent adverse events (≥20% of subjects in any group) for the Vc-MP, MP, and pooled single-agent Velcade treatment groups.

Table 6 - Incidence of Most Common (At Least 20% in Any Group) Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Multiple Myeloma SCS: Safety Analysis Set)

	---------- Previously Untreated ----------		Previously Treated
	Vc-MP	MP	VELCADE
MedDRA System Organ Class	(N=340)	(N=337)	(N=1033)
Preferred Term	n (%)	n (%)	n (%)
Total no. Subjects with TEAE	338 (99)	326 (97)	1031 (>99)
Blood and Lymphatic System Disorders	279 (82)	259 (77)	629 (61)
Anaemia	147 (43)	187 (55)	344 (33)
Leukopenia	113 (33)	100 (30)	75 (7)
Lymphopenia	83 (24)	58 (17)	51 (5)
Neutropenia	165 (49)	155 (46)	201 (19)
Thrombocytopenia	178 (52)	159 (47)	408 (39)
Gastrointestinal Disorders	262 (77)	185 (55)	907 (88)
Constipation	125 (37)	54 (16)	432 (42)
Diarrhoea	157 (46)	58 (17)	570 (55)
Nausea	164 (48)	94 (28)	593 (57)
Vomiting	112 (33)	55 (16)	359 (35)
General Disorders and Administration Site Conditions	239 (70)	199 (59)	862 (83)
Asthenia	73 (21)	60 (18)	205 (20)
Fatigue	98 (29)	86 (26)	486 (47)
Oedema Peripheral	68 (20)	34 (10)	196 (19)
Pyrexia	99 (29)	64 (19)	393 (38)
Metabolism and Nutrition Disorders	159 (47)	124 (37)	554 (54)
Anorexia	77 (23)	34 (10)	268 (26)
Nervous System Disorders	253 (74)	122 (36)	775 (75)
Headache	49 (14)	35 (10)	241 (23)
Neuralgia	121 (36)	5 (1)	77 (7)
Neuropathy Peripheral	11 (3)	1 (<1)	281 (27)
Peripheral Sensory Neuropathy	151 (44)	16 (5)	87 (8)
Psychiatric Disorders	112 (33)	76 (23)	411 (40)
Insomnia	69 (20)	43 (13)	208 (20)
Respiratory, Thoracic and Mediastinal Disorders	133 (39)	123 (36)	585 (57)
Cough	71 (21)	45 (13)	213 (21)
Dyspnoea	50 (15)	44 (13)	220 (21)
Skin and Subcutaneous Tissue Disorders	140 (41)	80 (24)	487 (47)
Rash	66 (19)	24 (7)	205 (20)

MedDRA=Medical Dictionary for Regulatory Activities; Vc-MP=VELCADE-melphalan-prednisone; MP=melphalan-prednisone; no.=number; TEAE=treatment emergent adverse event
Note: Percentages calculated with the number of subjects in each group as denominator.

- Serious adverse events and deaths

Deaths

Table 7 summarizes the all-cause mortality rates within 30 days after the last dose of study medication for the Vc-MP, MP, and single-agent Velcade treatment groups. Five percent of subjects treated with Vc-MP died within 30 days after their last dose (during treatment), compared with 4% of subjects treated with MP and 10% of subjects treated with single-agent Velcade. As the length of exposure was greater in Study MMY-3002 than in the prior studies, the incidence of death within 30 days of last dose was adjusted for length of exposure; the incidence rates for both Vc-MP and MP appeared to be

lower than for single-agent Velcade (0.006 vs. 0.005 vs. 0.019 events per patient-month, respectively). The incidence of treatment-related deaths was low for the Vc-MP, MP, and single-agent Velcade treatment groups (1%, 2%, and 1%, respectively). The exposure-adjusted incidence rate of treatment-related deaths was similar for all 3 treatment groups (0.002 vs. 0.002 vs. 0.003 events per patient-month, respectively).

Table 7 - Summary of All-Cause Mortality Within 30 Days After Last Dose (Multiple Myeloma SCS)

	Previously Untreated				Previously Treated	
	Vc-MP (N=340)		MP (N=337)		VELCADE (N=1033)	
Description	Unadjusted, n (%)	Exposure-adjusted[a]	Unadjusted, n (%)	Exposure-adjusted[a]	Unadjusted, n (%)	Exposure-adjusted[a]
Deaths within 30 days after last dose	18 (5%)	0.006	14 (4%)	0.005	103 (10%)	0.019
95% confidence interval[b]	3.167 - 8.311	0.003 - 0.008	2.290 - 6.959	0.003 - 0.008	8.212 - 11.97	0.016 - 0.023
Treatment-related deaths[c]	5 (1%)	0.002	6 (2%)	0.002	14 (1%)	0.003
95% confidence interval[b]	0.479 - 3.571	0.001 - 0.003	0.656 - 3.989	0.001 - 0.004	0.743 - 2.294	0.001 - 0.004
VELCADE-related deaths[d]	5 (1%)	0.002	0 (0%)	0.000	14 (1%)	0.003
95% confidence interval[b]	0.479 - 3.571	0.001 - 0.004	-	-	0.743 - 2.294	0.001 - 0.004

Vc-MP=VELCADE-melphalan-prednisone; MP=melphalan-prednisone

[a] Exposure-adjusted incidence rate equals the number of deaths divided by the sum of time to death/censoring (in patient-months).

[b] Confidence intervals were based on F-approximation for unadjusted incidence rates and chi-square approximation for exposure-adjusted incidence rate.

[c] For Study MMY-3002, it includes all deaths due to adverse events that were related to 1 of the 3 study drugs: VELCADE, melphalan, or prednisone. For Vc-MP group, censoring time is 30 days after last dose of any of the 3 study drugs.

[d] For Study MMY-3002, it includes those deaths due to adverse events that were related to VELCADE. For Vc-MP group censoring time is 30 days after last VELCADE dose.

Serious Adverse Events

The most frequent (≥2%) treatment-emergent serious adverse events are summarized in Table 8 for the Vc-MP and MP treatment groups in Study MMY-3002, as well as for single-agent Velcade use in prior studies. Serious adverse events were reported for 46% of subjects who received Vc-MP, compared with 36% of subjects who received MP and 52% of subjects who received single-agent Velcade. The Vc-MP and single-agent Velcade treatment groups were similar with respect to serious adverse events of anemia, thrombocytopenia, herpes zoster, diarrhea, nausea, and vomiting. Incidences of neutropenia (1% in both), leukopenia (<1% in both), and neuralgia (1% in the Vc-MP group and <1% in the single-agent Velcade group) also were similar between the 2 treatment groups.
The incidence of Velcade-related serious adverse events was similar with Vc-MP treatment (26%) and single-agent Velcade treatment (28%).

Table 8 - Incidence of Most Common (At Least 2% in Any Group) Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (Multiple Myeloma SCS: Safety Analysis Set)

	---------- Previously Untreated ----------		Previously Treated
MedDRA System Organ Class Preferred Term	Vc-MP (N=340) N (%)	MP (N=337) n (%)	VELCADE (N=1033) N (%)
Total no. Subjects with Serious TEAE	155 (46)	121 (36)	541 (52)
Blood and Lymphatic System Disorders	19 (6)	20 (6)	71 (7)
Anaemia	7 (2)	8 (2)	17 (2)
Febrile Neutropenia	3 (1)	7 (2)	9 (1)
Thrombocytopenia	13 (4)	8 (2)	33 (3)
Cardiac Disorders	21 (6)	19 (6)	59 (6)
Atrial Fibrillation	6 (2)	4 (1)	7 (1)
Gastrointestinal Disorders	46 (14)	17 (5)	124 (12)
Abdominal Pain	6 (2)	2 (1)	13 (1)
Diarrhoea	18 (5)	1 (<1)	53 (5)
Nausea	9 (3)	1 (<1)	29 (3)
Vomiting	12 (4)	1 (<1)	41 (4)
General Disorders and Administration Site Conditions	24 (7)	23 (7)	148 (14)
Asthenia	4 (1)	1 (<1)	20 (2)
Disease Progression	0	0	39 (4)
Pyrexia	12 (4)	11 (3)	65 (6)
Hepatobiliary Disorders	8 (2)	4 (1)	5 (<1)
Hepatic Function Abnormal	6 (2)	1 (<1)	0
Infections and Infestations	59 (17)	51 (15)	193 (19)
Herpes Zoster	6 (2)	2 (1)	21 (2)
Pneumonia	37 (11)	24 (7)	82 (8)
Sepsis	2 (1)	7 (2)	25 (2)
Urinary Tract Infection	6 (2)	0	5 (<1)
Metabolism and Nutrition Disorders	28 (8)	6 (2)	80 (8)
Dehydration	13 (4)	1 (<1)	40 (4)
Hypercalcaemia	1 (<1)	1 (<1)	17 (2)
Hyponatraemia	6 (2)	0	9 (1)
Musculoskeletal and Connective Tissue Disorders	13 (4)	9 (3)	53 (5)
Back Pain	3 (1)	3 (1)	17 (2)
Nervous System Disorders	16 (5)	8 (2)	93 (9)
Syncope	2 (1)	1 (<1)	17 (2)
Renal and Urinary Disorders	12 (4)	11 (3)	63 (6)
Renal Failure	2 (1)	3 (1)	34 (3)
Renal Failure Acute	4 (1)	3 (1)	16 (2)
Renal Impairment	3 (1)	8 (2)	4 (<1)
Respiratory, Thoracic and Mediastinal Disorders	20 (6)	17 (5)	90 (9)
Dyspnoea	7 (2)	6 (2)	34 (3)
Vascular Disorders	15 (4)	8 (2)	49 (5)
Hypotension	6 (2)	1 (<1)	18 (2)
Orthostatic Hypotension	2 (1)	0	16 (2)

MedDRA=Medical Dictionary for Regulatory Activities; Vc-MP=VELCADE-melphalan-prednisone; MP=melphalan-prednisone; no.=number; TEAE=treatment emergent adverse event
Note: Percentages calculated with the number of subjects in each group as denominator.

- Safety in special populations

Subgroup analyses were performed with respect to adverse events to evaluate the safety of Vc-MP in different special populations. These analyses showed a similar safety profile across age and gender. For the Vc-MP regimen, the adverse event profile for subjects with moderate renal function impairment (30 to 60 mL/min creatinine clearance) was similar to the profile for subjects without renal function impairment (>60 mL/min creatinine clearance).

- Discussion on clinical safety

The safety profile of Velcade in combination with MP in Study MMY-3002 was consistent with the known safety profiles of both Velcade and MP. No new safety concerns emerged for Vc-MP relative to what has been observed for each of its components. The safety profile of MP was as expected in this patient population: major side effects of MP were consistent with those described in previous studies. The safety profile was comparable between Vc-MP and single-agent Velcade used in prior studies, despite the older patient population in the Vc-MP treatment group as compared with the single-agent VELCADE treatment group (median age, 71 and 60 years, respectively).

The most frequently reported adverse events for the Vc-MP treatment group were as expected based on the known toxicity profile of each of the 3 individual agents. Although peripheral neuropathy events were more common with Vc-MP treatment than with single-agent Velcade treatment (47% vs. 37%, respectively), the incidence of Grade ≥3 peripheral neuropathy events was similar (13% and 11%) and serious events were uncommon for both groups (1% each). Exposure-adjusted incidence rates, as well as relationship to cumulative dose and time to onset of peripheral neuropathy events, were similar between treatment groups. The reversibility of peripheral neuropathy has been documented in the majority of cases for subjects receiving Vc-MP (74% improvement or recovery). The addition of MP to VELCADE treatment did not appear to affect the cumulative dose at onset or the time to onset of peripheral neuropathy events.

Overall, the number of serious adverse events was 10% higher in the VC-MP group than in the MP group in this study as well as the number of deaths and adverse events Grade>3. Particularly, in the beginning of the treatment (Cycles 1-4) there were more adverse events in the Vc-MP group than in the control group. However, during the next cycles (5-9) the tolerability of Vc-MP treatment was similar to that of MP treatment group. Therefore, no new safety concerns arise with the longer duration of treatment of 54 weeks. The safety results of this study have been included in section 4.8 of the SPC.

3. Summary of the Risk Management Plan

The MAH submitted a Risk Management Plan.

Safety Concern	**Proposed Pharmacovigilance Activities (routine and additional)**	**Proposed Risk Minimisation Activities (routine and additional)**
Heart failure	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. It a phase III randomized, comparative study the incidence of heart failure in the VELCADE treatment group was similar to that in the dexamethasone group. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored. • SmPC: Labelled in Section 4.8 (Undesirable effects)

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Abnormal liver function tests (including hepatitis)	• Routine pharmacovigilance	• SmPC: Language in Section 4.2 regarding use in patients with impaired hepatic function • SmPC: Contraindications: Severe hepatic impairment • SmPC: Special warnings and precautions for use: Hepatic impairment - Patients with hepatic impairment should be treated with extreme caution and a dose reduction should be considered (see sections 4.2 and 4.3). Hepatic Reactions - Rare cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib (see Section 4.8). • SmPC: Labelled in Section 4.8 (Undesirable effects) **Additional activities** • A pharmacokinetic and safety study in patients with hepatic impairment is ongoing. (CTEP 6432)
Acute hypersensitivity reactions	• Routine pharmacovigilance	• SmPC: Contraindications: Hypersensitivity to bortezomib, boron, or to any of the excipients. • SmPC: Labelled in Section 4.8 (Undesirable effects)
Tumour lysis syndrome	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: Because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. • SmPC: Labelled in Section 4.8 (Undesirable effects)
Motor peripheral neuropathy (including paralysis)	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: Language regarding the risk of peripheral neuropathy when administered VELCADE. • SmPC: Labelled in Section 4.8 (Undesirable effects)

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Autonomic neuropathy	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: Peripheral Neuropathy - In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited. • SmPC: Labelled in Section 4.8 (Undesirable effects)
Acute diffuse infiltrative pulmonary disease	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: Language regarding the risk of ADIPD when administered VELCADE. • SmPC: Labelled in Section 4.8 (Undesirable effects) **Additional activities** Periodic Ad hoc International Pulmonary Advisory Boards to review cases of potential ADIPD are ongoing. • An ongoing Japanese PMS survey (VEL-PMS- JPN-1) has specific focus on pulmonary complications associated with VELCADE treatment.
Pericardial disease	• Routine pharmacovigilance	• SmPC: Contraindications: Pericardial disease • SmPC: Labelled in Section 4.8 (Undesirable effects)
Pulmonary hypertension	• Routine pharmacovigilance	• SmPC: Labelled in Section 4.8 (Undesirable effects)
Ventricular rhythm abnormalities	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: ECG Investigations – There have been isolated cases of QT-interval prolongation in clinical studies, causality has not been established. • SmPC: Labelled in Section 4.8 (Undesirable effects)

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Hepatic failure	• Routine pharmacovigilance	• SmPC: Language in Section 4.2 regarding use in patients with impaired hepatic function • SmPC: Contraindications: Severe hepatic impairment • SmPC: Special warnings and precautions for use: Hepatic impairment - Patients with hepatic impairment should be treated with extreme caution and a dose reduction should be considered (see sections 4.2 and 4.3). Hepatic Reactions - Rare cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib (see Section 4.8). • SmPC: Labelled in Section 4.8 (Undesirable effects) **Additional activities** • A pharmacokinetic and safety study in patients with hepatic impairment is ongoing. (CTEP 6432)
Immunocomplex-mediated reactions (including serum sickness, glomerulonephritis)	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: Potentially immunocomplex-mediated reactions - Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. Bortezomib should be discontinued if serious reactions occur. • SmPC: Labelled in Section 4.8 (Undesirable effects)
Amyloidosis	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: The impact of proteasome inhibition by bortezomib on disorders associated with protein accumulation such as amyloidosis is unknown. Caution is advised in these patients. **Additional activities** • Ongoing safety study evaluation (26866138-CAN-2007)
Guillain-Barré Syndrome	• Routine pharmacovigilance	

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Reversible posterior leukoencephalopathy syndrome	• Routine pharmacovigilance	
Central nervous system disorders other than RPLS (encephalopathy, dementia, Parkinson's disease)	• Routine pharmacovigilance	
Use in patients with hepatic impairment	• Routine pharmacovigilance	• SmPC: Language in Section 4.2 regarding use in patients with impaired hepatic function • SmPC: Contraindications: Severe hepatic impairment • SmPC: Special warnings and precautions for use: Hepatic impairment - Patients with hepatic impairment should be treated with extreme caution and a dose reduction should be considered (see sections 4.2 and 4.3). **Additional activities** • A pharmacokinetic and safety study in patients with hepatic impairment is ongoing. (CTEP 6432)
Use in patients with renal impairment	• Routine pharmacovigilance	• SmPC: Special warnings and precautions for use: The incidence of serious undesirable effects has been shown to increase in patients with mild to moderate renal impairment compared to patients with normal renal function (see Section 4.8). Renal complications are frequent in patients with multiple myeloma. Such patients should be monitored closely and dose reduction considered. • SmPC: Labelled in Section 4.8 (Undesirable effects) Data from the CTEP NCI-5874 study were submitted as part of variation EMEA/H/C/539/II/29, a variation supporting an update to posology for patients with renal impairment. This was submitted on 11 April 2008 and the review of this is ongoing. **Additional activities** • Ongoing safety study (CTEP 5874)

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Similarity with authorised orphan medicinal products

According to Article 3 of the Commission Regulation (EC) No 847/2000, for the purposes of the implementation of Article 8, "Similar active substance" means an identical active substance, or an active substance with the same principal molecular structural features (active moiety) and which acts via the same mechanism. Thus the similarity assessment takes into account molecular structural features, mechanism of action and therapeutic indication.

The Applicant has provided a report discussing the issue of similarity with the orphan medicinal products Revlimid (lenalidomide) and Thalidomide Pharmion (thalidomide) authorised for the treatment of multiple myeloma.

Having considered the arguments presented by the MAH of Velcade, the CHMP concluded that bortezomib does not share the same principal molecular structural features as lenalidomide and thalidomide and the differences in molecular structure are not only minor. The mechanism of action of bortezomib is also different than those of thalidomide and lenalidomide.

Therefore, the CHMP is of the opinion that Velcade is not similar to any authorised orphan medicinal products within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. Benefit-Risk Assessment

Velcade is currently indicated as monotherapy 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. The applicant has now performed one clinical study to show the efficacy of Velcade in combination for the treatment of patients with previously untreated multiple myeloma, i.e. in a first-line indication.

Study MMY-3002 was designed to determine whether the addition of Velcade to standard MP therapy would improve the outcome of previously untreated patients with multiple myeloma. The efficacy of Velcade and of MP was well established and both therapies were widely used to treat multiple myeloma. The MAH has also discussed thoroughly the benefits and risks of all the standard chemotherapies and the choice of MP as a comparator is well justified. The choice of endpoints was considered adequately justified.

The results of all the endpoints consistently showed that Vc-MP was superior to the MP treatment. Vc-MP-treated subjects showed significant improvements over MP-treated subjects in TTP, PFS, OS, OR rate, CR rate, time to response, and time to subsequent myeloma therapy. Treatment effect was maintained across all subgroups tested. Additionally, responding subjects in the Vc-MP group experienced substantially longer duration of response relative to the MP treated subjects. In addition, the time to subsequent therapy was extended, allowing patients to experience more time without multiple myeloma treatment. There was also an improvement in myeloma-related complications. These results are supportive of the clinical superiority of Vc-MP treatment compared to MP treatment.

The safety profile of Velcade in combination with MP in Study MMY-3002 was consistent with the known safety profiles of both Velcade and MP. No new safety concerns emerged for Vc-MP relative to what has been observed with the three individual components.

Overall, the benefit-risk of Velcade in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant is considered positive. Section 4.1 of the SPC is updated to include this new indication.