21 November 2013
EMA/CHMP/775037/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VELCADE

International non-proprietary name: **BORTEZOMIB**

Procedure No. EMEA/H/C/000539/II/0063/G

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of abbreviations

ASCT	autologous stem cell transplantation
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CR	complete response
CT	computed tomograpy
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EU	European Union
HR	hazard ratio
IDM/RC	Independent Data Monitoring/Review Committee
IDMC	Independent Data Monitoring Committee
IMWG	International Myeloma Working Group
ISS	International Staging System
IV	intravenous(ly)
M-protein	myeloma protein
MR	marginal response
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nCR	near complete response
ORR	overall response rate
OS	overall survival
PD	disease progression
PFS	progression-free survival
PPE	palmar-plantar erythrodysesthesia syndrome
PR	partial response
SC	subcutaneous(ly)
SCE	Summary of Clinical Efficacy

SCS	Summary of Clinical Safety
SD	stable disease
SmPC	Summary of Product Characteristics
TTP	Time to (disease) progression
US	United States
Vc+Dex	VELCADE plus dexamethasone
Vc+DOXIL	VELCADE plus DOXIL
VDC	VELCADE plus dexamethasone plus cyclophosphamide
VDL	VELCADE plus dexamethasone plus lenalidomide
VGPR	very good partial response

1. Background information on the procedure

1.1. Type II and group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 28 September 2012 an application for a group of variations including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
VELCADE	BORTEZOMIB	See Annex A

The following variations were requested in the group:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extensions of indication for Velcade in combination with pegylated liposomal doxorubicin or in combination with dexamethasone in patients with relapsed and /or progressive multiple myeloma who have received at least 1 prior therapy. Consequently, the MAH proposed updates of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC as well as editorial changes. The Package leaflet was proposed to be updated accordingly.

The group of variations proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Melchiorri Co-Rapporteur: Outi Mäki-Ikola

Submission date:	28 September 2012
Start of procedure:	19 October 2012
Rapporteur's preliminary assessment report circulated on:	15 December 2012
CoRapporteur's preliminary assessment report circulated on:	11 December 2012
PRAC RMP advice and assessment overview adopted by PRAC on :	10 January 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	17 January 2013
The CHMP adopted a report on similarity of Velcade with Thalidomide Celgene & Revlimid on:	17 January 2013
MAH's responses submitted to the CHMP on:	24 April 2013
Rapporteur's and CoRapporteur's joint preliminary assessment report on the MAH's responses circulated on:	27 May 2013
Rapporteur's and CoRapporteur's joint updated assessment report on the MAH's responses circulated on:	24 June 2013
PRAC RMP advice and assessment overview adopted by PRAC on :	13 June 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	27 June 2013
MAH's responses submitted to the CHMP on:	18 July 2013
Rapporteur's and CoRapporteur's joint assessment report on the MAH's responses circulated on:	23 August 2013
PRAC RMP advice and assessment overview adopted by PRAC on :	5 September 2013
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	19 September 2013
The CHMP adopted an updated report on similarity of Velcade with Thalidomide Celgene, Revlimid and Imnovid on (Appendix 2):	19 September 2013
MAH's responses submitted to the CHMP on:	18 October 2013
Rapporteur's and CoRapporteur's joint assessment report on the MAH's responses circulated on:	31 October 2013
PRAC RMP advice and assessment overview adopted by PRAC on	7 November 2013
Rapporteur's and CoRapporteur's joint updated assessment report on the MAH's responses circulated on:	15 November 2013
CHMP Opinion	21 November 2013

2. Scientific discussion

2.1. Introduction

Multiple Myeloma (MM) (also known as plasma cell myeloma) is a progressive rare 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 only (free immunoglobulin monoclonal κ and λ light chains). Multiple myeloma usually manifests as 1 or more lytic bone lesions, monoclonal protein in the blood or urine, and disease in the bone marrow.

Chemotherapy is indicated for patients with newly diagnosed symptomatic myeloma, with age, performance status, and neurologic and comorbidity conditions being critical factors in the choice of initial therapy. With standard chemotherapeutic agents, median survival time is approximately 3 years from diagnosis but the use of autologous stem cell transplantation (auto-SCT) has increased median survival to 5 years for patients less than 65 years of age. Nevertheless, MM remains an incurable disease, and almost all patients will eventually relapse and die from this disorder. In the absence of a definitive cure for multiple myeloma, the current goal of treatment is to improve patients' long-term outcomes, such as progression-free survival (PFS) and overall survival. One important factor that has been associated with prolonged PFS and overall survival is the magnitude of response to treatment, particularly achievement of CR.

In patients who are candidates for auto-SCT, induction treatment before auto-SCT with combination regimens containing at least 1 novel agent (i.e. bortezomib, thalidomide, lenalidomide), followed by high dose chemotherapy with melphalan and subsequent single or tandem ASCT is the recommended treatment option.

Despite successful first-line treatment, virtually all patients will eventually relapse/progress, or become refractory to treatment. For patients with relapsed or refractory disease, the ultimate goal of therapy is still to achieve the best possible response. Data from clinical studies have shown that, similar to newly diagnosed patients, the quality and magnitude of response in patients with relapsed or refractory multiple myeloma are associated with clinical benefit and better long-term outcomes.

Multiple myeloma relapsing after allogeneic stem cell transplantation (allo-SCT) has a poor outcome.

VELCADE (bortezomib) as monotherapy is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.

There is a growing body of clinical evidence from company-sponsored and independently conducted studies, as well as reports in the literature, that VELCADE in combination with other agents improves the efficacy of treatment for patients with relapsed/progressive or refractory multiple myeloma.

Anthracyclines, particularly doxorubicin, are widely used in the front-line setting to treat multiple myeloma. It has been shown that proteasome inhibitors enhance chemosensitivity and that the combination of an anthracycline with a proteosome inhibitor enhances antitumor activity in solid tumors and multiple myeloma models. However, cumulative doses of traditional doxorubicin are associated with increased cardiotoxicity. The pegylated liposomal formulation of doxorubicin, was designed to enhance the efficacy and reduce the dose-limiting toxicities of doxorubicin by altering the plasma pharmacokinetics and selective tissue distribution of the drug. Because of its reduced cardiotoxicity potential, Caelyx was selected as the anthracycline of choice to combine with VELCADE for the treatment of patients with progressive disease.

The **combination of Velcade with pegylated liposomal doxorubicin** (Caelyx from the same MAH of Velcade, Janssen Cilag) with Velcade was approved in 2007 within the variation II/45 for Caelyx in which the Applicant had already submitted this pivotal clinical study, MMY-3001 to demonstrate the efficacy of Caelyx when combined with Bortezomib, compared to Bortezomib monotherapy, in subjects with relapsed or refractory multiple myeloma. As a result of the approval of such extension of indication for Caelyx, the CHMP sent, in July 2011, a letter to the MAH of Velcade (the same for both products) recommending the submission of a variation for VELCADE to update the product information with regard to its use in combination with pegylated liposomal doxorubicin.

The **combination of Velcade with dexamethasone** has also been shown to improve response in subjects who had an initially poor response to VELCADE monotherapy. Currently, the combination of Velcade to Dexamethasone is considered a standard clinical practice. In several clinical studies, although not foreseen in the study object, dexamethasone was allowed at the discretion of the investigator.

Consequently, the MAH of Velcade has submitted this group of variations to extend the indication of Velcade as follows (new text underlined, deleted text strikethrough):

"VELCADE as monotherapy or in combination with pegylated liposomal-doxorubicin or dexamethasone is indicated for the treatment of adult patients with relapsed and/or progressive multiple myeloma who have received at least 1 prior therapy ~~and who have already undergone or are unsuitable for bone marrow transplantation~~."

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

As this change of indication will align the product information with current medical practice, the MAH did not expect an increase in the environmental exposure of bortezomib following the approval of this variation. This was agreed by the CHMP.

Bortezomib and/or its metabolites are unlikely to represent a risk to the environment following prescribed usage in patients.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of Studies Included in the VELCADE Combination Submission

Key Studies	Design / Study Participants	Treatment Groups	No. Enrolled Subjects
Study MMY-3001	Phase 3 randomized, parallel-group, open-	Group A: Vc IV 1.3 mg/m^2 twice weekly on Days 1, 4, 8, and 11 of	Group A: 322 Group B: 324

	label, international, multicenter/men and women, ≥18 years of age with previously treated R/R MM, ECOG PS 0 or 1 Primary efficacy endpoint: time to progression	each 21-day cycle Group B: Vc (as above) + CAELYX/DOXIL IV 30 mg/m^2 on Day 4 of each 21-day cycle	
Study MMY-2045 Newly submitted	Phase 2, randomized parallel-group open-label, international, multicenter (Part 1: nonrandomized for initial 4 cycles; Part 2: randomized for up to 4 additional cycles)/men and women, ≥18 years of age with previously treated R/R MM, Karnofsky PS ≥60 Primary efficacy endpoint: ORR (CR+VGPR+PR)	Part 1 (nonrandomized treatment - all subjects): Group A: Vc IV 1.3 mg/m^2 twice weekly on Days 1, 4, 8, and 11 + Dex 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle Part 2 (subjects with SD were randomized to Group B, C, or D below; subjects with ≥PR continued as in Group A) Group B: Vc + Dex (as above), or Group C: Vc + Dex (as above) + cyclophosphamide 500 mg orally on Days 1, 8, and 15 of each 21-day cycle, or Group D: Vc + Dex (as above) + lenalidomide 10 mg orally on Days 1 through 14 of each 21-day cycle	Part 1: 163 enrolled and treated Part 2 Group A: 144 Group B: 7 Group C: 8 Group D: 4
Supportive Study			
Study MMY-3021	Phase 3, randomized (2:1, SC:IV), open-label, international, multicenter/ men and women, ≥18 years of age with previously treated, R/R MM, Karnofsky PS ≥70 Primary efficacy endpoint: ORR (CR+PR) after 4 cycles of treatment	Group A: Vc IV 1.3 mg/m^2 twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle Group B: Vc SC (same dose and schedule as Group A) Subjects with NC or PR after 4 cycles could receive add-on dexamethasone 20 mg orally on the day of and day after Vc	Group A: 74 Group B: 148 Vc monotherapy: 101 Vc+Dex: 121

CR=complete response; Dex=dexamethasone; ECOG=Eastern Cooperative Oncology Group; IV=intravenous(ly); MM=multiple myeloma; NC=no change; ORR=overall response rate; PR=partial response; PS=performance status; R/R=relapsed/refractory; SC=subcutaneous(ly); SD=stable disease; Vc=VELCADE; VGPR=very good partial response

2.3.2. Clinical pharmacology

No formal evaluations of the clinical pharmacology and dose finding of VELCADE in combination with pegylated liposomal doxorubicin (Caelyx) or dexamethasone have been performed.

Two published references were included in this application to support the chosen Velcade, Caelyx and dexamethasone dosages.

A Phase 1 study (Orlowski RZ Vorhees PM, Garcia RA, et al. Phase I trial of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with advanced hematologic malignancies. Blood 2005; 105:3058-3065) conducted in 42 subjects with advanced hematologic malignancies, including multiple myeloma, showed that the combined administration of VELCADE and CAELYX/DOXIL did not alter the pharmacokinetics of CAELYX/DOXIL.

A Phase I study (Hellman A, Rule S, Walewski J. Effect of cytochrome P450 3A4 inducers on the pharmacokinetic, pharmacodynamic and safety profiles of bortezomib in patients with multiple myeloma or non-Hodgkin's lymphoma. Clin Pharmacokinet 2011; 50(12):781-791) showed that in 18 subjects, 13 of whom had relapsed or refractory multiple myeloma, who received treatment with a combination of bortezomib (1.3 mg/m^2 IV on Days 1, 4, 8, and 11 every 3 weeks) plus dexamethasone (40 mg orally on Days 1 through 4 and 9 through 12 of Cycle 3), the co-administration of dexamethasone did not affect the bioavailability of VELCADE.

2.3.3. Discussion on clinical pharmacology

While evidence from a published phase 1 study showed that bortezomib, a weak inhibitor of the cytochrome P450 isozymes 1A2, 2C9, 2C19, 2D6 and 3A4, did not alter the PK of Caelyx, no information is available for PK parameters of bortezomib when administered with Caelyx. Moreover, the pharmacokinetic parameters of doxorubicin from different dose levels were pooled together when administered together with bortezomib, and the pharmacokinetic parameters of doxorubicin when bortezomib was not given were not presented in the publication. Based on the presented literature the effect of the co-administration of bortezomib and doxorubicin on pharmacokinetics of both drugs remains still unclear.

As regards dexamethasone, the co-administration of dexamethasone, a weak CYP 3A4 inducer, did not have significant effect on exposure of bortezomib. The AUCs of bortezomib with and without concomitant dexamethasone were comparable based on the literature reference.

Considering that in study MMY-2045 dexamethasone was given at a lower dose level (20 mg) vs 40 mg administered in the cited published Phase 1 study, no significant alteration of the Velcade PK is expected by the co-administration with dexamethasone. Moreover, currently in the Velcade SmPC section 4.5 it is reported:

“In the same drug-drug interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 7 patients.”

2.3.4. Conclusions on clinical pharmacology

No formal pharmacokinetic and pharmacodynamics studies are available for bortezomib when administered together with doxorubicin or dexamethasone,. However, this is acceptable as clinical efficacy and safety data have been submitted to support this application.

2.4. Clinical efficacy

2.4.1. Main studies

Study MMY-3001 (combination with pegylated liposomal doxorubicin)

This study was previously submitted and assessed by the CHMP for the extension of indication of Caelyx (pegylated liposomal doxorubicin) in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have undergone or are unsuitable for bone marrow transplant (EMEA/H/C/000089/II/0045, Commission Decision on 14 December 2007). Methods and results are summarised in this report, with further details available in the CHMP Assessment report of the Caelyx variation.

Methods

Study MMY-3001 was a Phase III, randomized, parallel-group, open-label, active-controlled multi-centre study. The aim was to compare the safety and efficacy of Caelyx/Bortezomib combination therapy with Bortezomib monotherapy in adult subjects with multiple myeloma, whose disease has progressed after at least one regimen of prior chemotherapy or was refractory to initial treatment.

The primary endpoint was time to progression (TTP). The secondary endpoints were OS and response rate.

The sample size for the study was estimated by assuming that the time to progression on the Bortezomib monotherapy arm was 6 months. An improvement in median time to progression from 6 months to 7.8 months was considered to be clinically relevant. This corresponds to a hazard ratio of 1.3.

Results

646 subjects were randomly assigned 1:1 to treatment with Caelyx/Bortezomib combination therapy (n=324) or Bortezomib monotherapy (n=322).

The median number of cycles received was 5 and the median duration of treatment was approximately 3.5 months in both arms

Primary endpoint

At the planned interim analysis (cut-off April, 2006), the median TTP was 6.5 months in bortezomib arm vs 9.3 months in the Caelyx-bortezomib arm (gain of 2.8 months; HR 1.82 CI [1.41, 2.35], P=0.000004).

At an unplanned TTP and survival analysis requested by the FDA (cut-off November 2006), the median TTP was 6.9 months in the bortezomib arm and 8.9 months in the Caelyx-bortezomib arm (gain of 2 months; HR=1.55 CI [1.27, 1.89], p=0.000013). Based on these results it was decided to stop rule defined for the initial interim analysis.

Secondary endpoint

At the time of the pre-planned interim analysis, 12% of subjects (39) in the Bortezomib arm and 9% (28) of subjects in the Caelyx-bortezomib arm had died (p=0.113 stratified log-rank test, hazard ratio = 1.48 with 95% CI [0.91, 2.41]). The trend was in favour of the combination group but statistical significance had not been achieved.

At the time of the unplanned interim analysis, a total of 139 deaths, 81 subjects in the Bortezomib arm and 58 in the Caelyx-bortezomib arm, and a median follow-up of 10.9 months and a mortality risk reduction point estimate of 29% (hazard ratio [95%CI]:1.406 [1.002 to 1.972]). This was an unplanned analysis (albeit requested by the FDA), so the precise interpretation of p-values was difficult, but the p-value was less than 0.048. Hence if this had been the final analysis a benefit in overall survival would have been shown.

As regards the ORR, 43% subjects (95% CI: 37.3; 48.6) achieved a complete or partial response in the Bortezomib arm compared with 48% subjects (95% CI: 41.8; 53.3) in the Caelyx-bortezomib arm (p=0.2514).

An unplanned survival update to allow assessment of the latest available data was requested by the CHMP in order to confirm the positive result in the primary endpoint TTP in the context of overall clinical benefit. As data cut off August 2007, an additional 67 deaths (38 in the Caelyx-bortezomib arm and 29 in the bortezomib arm) were reported (HR=0.86 CI: 0.649; 1.127) with 14% risk reduction.

Table 2: Summary of the overall survival analyses

	Planned Analysis	FDA-Mandated Update	CHMP-Mandated Update
Clinical data collection cut-off date	28 APR 2006	28 NOV 2006	10 AUG 2007
Median follow-up (months)	3.9	10.9	18.0
No. of death events (% of ITT)	67 (10%)	139 (22%)	206 (32%)
No. of deaths in test arm	28	58	96
No. of deaths in control arm	39	81	110
Hazard ratio[a] (95% CI)	0.68 (0.415 - 1.098)	0.71 (0.507 - 0.998)	0.86 (0.649 – 1.127)
Risk reduction	32%	29%	14%
P value (stratified log-rank test)	0.113	0.0476	0.265

CI = confidence interval; ITT = intent-to-treat; PLD = pegylated liposomal doxorubicin.

a: Hazard ratio <1 is in favor of the PLD + bortezomib arm.

Study MMY-2045 (combination with dexamethasone)

Methods

Study MMY-2045 was a Phase 2, multicentre, randomised, open-label, parallel group study in subjects with multiple myeloma who were refractory to or had relapsed/progressed after their primary therapy for multiple myeloma.

Study participants

The population included men and women ≥18 years of age with relapsed/progressive or refractory multiple myeloma after 1 prior therapy and a Karnofsky Performance Status (KPS) of ≥60%.

Subject had a life expectancy estimated at screening of at least 6 months.

Measurable secretory multiple myeloma: measurable disease for secretory multiple myeloma was defined by at least one of the following measurements: serum M-protein greater than or equal to 1 g/dl (≥10 gm/l) [10 g/l], urine M-protein of ≥200 mg/24 hours.

Among the exclusion criteria there were:

- Subject received more than one previous line of therapy for multiple myeloma.

- Subject has peripheral neuropathy or neuropathic pain of grade 2 or greater intensity.
- Subject had a myocardial infarction within 6 months of enrolment or has New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

Treatments

The study involved the use of Velcade in combination with dexamethasone (VD), followed by VD, VD plus cyclophosphamide (VDC), or VD plus lenalidomide (VDL).

The study consisted of two sequential parts.

In Part 1, patients received a combination of VD. Based on the response to this treatment, further study treatment (Part 2) was customized.

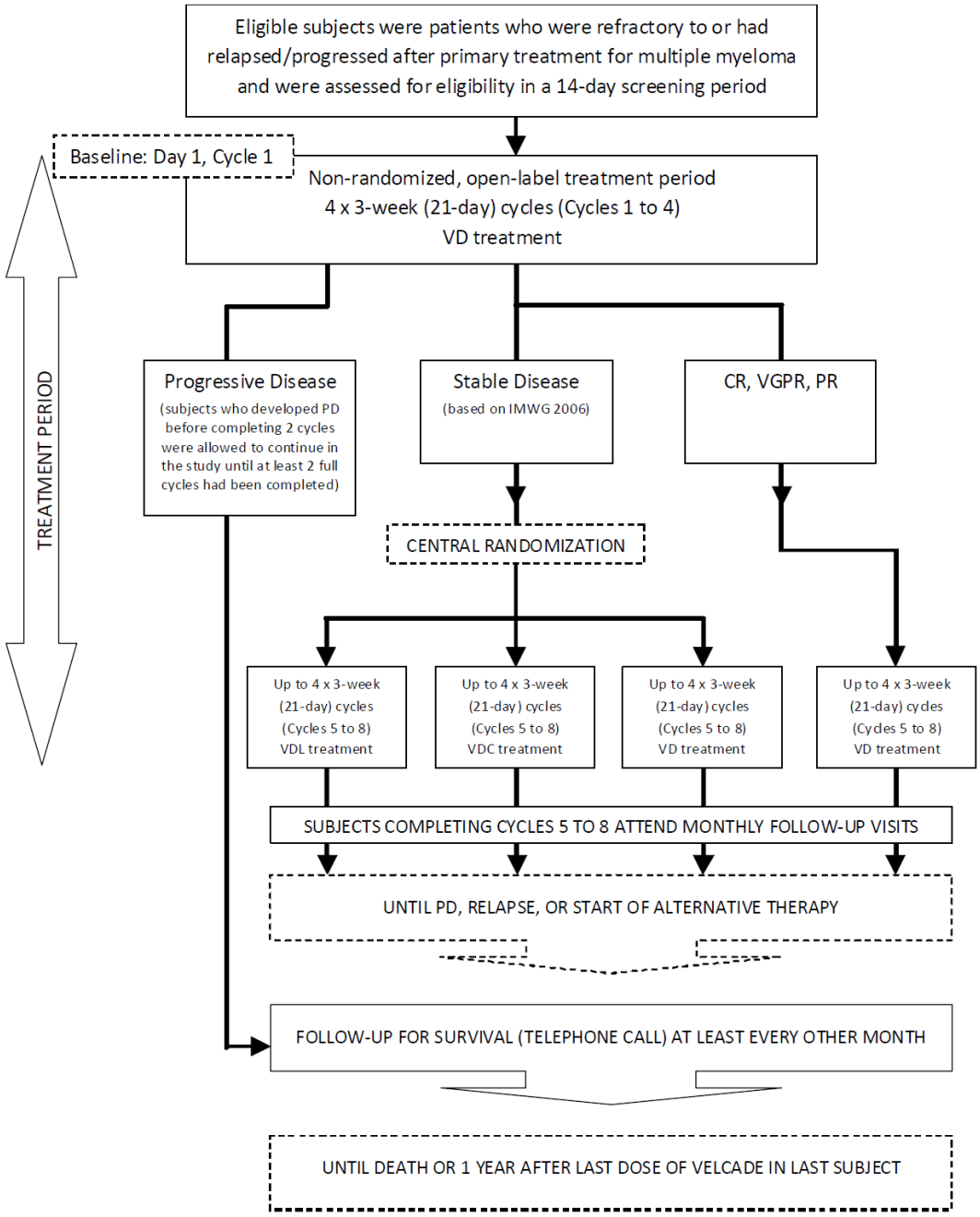
In Part 2:

i) subjects with a complete, a very good partial or a partial response continued to receive VD for a maximum additional 4 cycles, to an overall maximum of 8 cycles.

ii) subjects achieving stable disease, as defined by International Myeloma Working Group 2006 response criteria, underwent a central randomisation to treatment with VD or VDC or VDL. The randomization was stratified by age (65 years or more versus less than 65 years) and country. After randomization, subjects received up to an additional 4 (3-week) cycles of treatment.

The mode of administration of each treatment was:

- VELCADE 1.3 mg/m² intravenous bolus on Days 1, 4, 8 and 11; 3-week cycle.
- Dexamethasone 20 mg orally daily, on Days 1 2, 4, 5, 8, 9, 11 and 12;
- Cyclophosphamide 500 mg, orally daily, on Days 1, 8 and 15;
- Lenalidomide 10 mg orally daily, on Days 1 to 14.



Abbreviations: CR = complete response, PR = partial response, SD = stable disease, VD = VELCADE + dexamethasone, VDC = VELCADE + dexamethasone + cyclophosphamide, VDL = VELCADE + dexamethasone + lenalidomide, VGPR = very good partial response.

Figure 1 – Overview of the clinical study

Objectives

The primary objective was to assess the efficacy of adding either cyclophosphamide or lenalidomide in a randomized way to VELCADE-dexamethasone. The efficacy response was measured by the response rate of the disease.

Outcomes / endpoints

The primary efficacy endpoint was ORR as defined by the combination of subjects with CR, VGPR and PR during study and before the start of further therapies for multiple myeloma according to the IMWG criteria (Table 3).

Table 3: IMWG uniform response criteria by response subcategory for multiple myeloma

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	Not meeting criteria for CR, VGPR, PR, or PD	Increase of 25% from lowest response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio *and*	≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria		Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or*

Secondary efficacy endpoints were defined as below:

- TTR: Time from start of treatment to the date of the first documentation of a confirmed response.
- DOR: Applied to subjects achieving at least PR by the IMWG criteria and was measured from the start of achieving PR (first observation of PR before confirmation) to the time of disease progression or relapse from CR, with deaths owing to causes other than progression not counted, but censored.
- TTP: Time from start of treatment to the date of the first observation of disease progression or relapse from CR. Deaths owing to causes other than progression were not counted, but censored.
- PFS: Time from start of treatment to date of disease progression, relapse from CR or death.
- OS: Time interval from start of treatment to the date of death due to any cause. In the absence of confirmation of death (including subjects lost to follow-up), survival time was censored at the last date the subject was known to be alive.
- One-year survival: The proportion of subjects with a one year survival since the start of treatment (based on the Kaplan-Meier estimation).

Efficacy was evaluated (at Day 1 of Cycles 1 to 8 and End of Treatment) as the measurement of M-protein in serum and urine, until disease progression or relapse.

Sample size

The sample size for each treatment arm was calculated based on Fleming Single Stage procedure. The assumption was that if the overall response to treatment was 20% this would be considered worthwhile to be investigated further and that the minimal expected response rate of interest was 7.5%. With a power of 80% and alfa=5%, 38 subjects were required per treatment arm. Thus, a total of 114 subjects needed to be randomized. Based on the assumption that around 60% of the subjects would have SD after 4 cycles of Velcade and dexamethasone, it was estimated that at least 190 subjects needed to be enrolled in the study.

Randomisation

After having received 4 cycles of VD, subjects with SD as best response were randomized. It was assumed that 60% of the subjects enrolled in the study would be available for randomization. Within this subpopulation it was assumed that an additional 20% would show a response of at least PR.

Blinding (masking)

Not applicable.

Statistical methods

Since randomization occurred after 4 cycles of treatment, the population was referred to as the modified intent-to-treat (mITT=all subjects who received at least 1 dose and who had at least 1 post baseline efficacy assessment were included in the analysis) rather than the intent-to-treat population (PP=all mITT subjects without major protocol deviations).

The primary analysis population was the mITT population.

The safety analysis was performed using the safety analysis set.

A preplanned interim analysis of efficacy and safety was performed when all subjects had completed 4 cycles of VD (clinical cutoff date of 30 April 2010). An additional efficacy and safety analysis was performed after all subjects had reached the end of treatment (clinical cutoff date of 1 July 2011). The final analysis was performed at the end of the follow-up period (clinical cutoff of 2 August 2011).

Results

Participant flow

Recruitment

Study Period: 12 May 2008 to 2 August 2011

Conduct of the study

There were 2 amendments to the protocol.

Baseline data

The following table summarises demographic data.

Table 4: Summary of Demographic Data (Study MMY-2045: mITT population)

	Non-randomized		Randomized		Total	
	VD N=144		VD, VDC, VDL N=19		N=163	
Country, n (%)						
France	18	(12.5)	2	(10.5)	20	(12.3)
Germany	15	(10.4)	0		15	(9.2)
Greece	20	(13.9)	3	(15.8)	23	(14.1)
Hungary	0		2	(10.5)	2	(1.2)
Lithuania	9	(6.3)	0		9	(5.5)
Poland	17	(11.8)	2	(10.5)	19	(11.7)
Serbia	11	(7.6)	4	(21.1)	15	(9.2)
Spain	16	(11.1)	4	(21.1)	20	(12.3)
Turkey	19	(13.2)	0		19	(11.7)
United Kingdom	19	(13.2)	2	(10.5)	21	(12.9)
Total	144	(100.0)	19	(100.0)	163	(100.0)
Age at screening (years)						
n	144		19		163	
Mean (standard deviation)	64.3 (11.0)		59.9 (11.5)		63.8 (11.1)	
Median	64.5		60.0		63.0	
Range	41 - 86		34 - 83		34 - 86	
Age category (years), n (%)						
[30-44]	3	(2.1%)	1	(5.3%)	4	(2.5%)
[45-54]	32	(22.2%)	4	(21.1%)	36	(22.1%)
[55-64]	37	(25.7%)	8	(42.1%)	45	(27.6%)
[65-74]	42	(29.2%)	5	(26.3%)	47	(28.8%)
[75-84]	27	(18.8%)	1	(5.3%)	28	(17.2%)
>=85	3	(2.1%)	0		3	(1.8%)
Total	144	(100.0%)	19	(100.0%)	163	(100.0%)
Sex, n (%)						
Male	78	(54.2%)	8	(42.1%)	86	(52.8%)
Female	66	(45.8%)	11	(57.9%)	77	(47.2%)
Total	144	(100.0%)	19	(100.0%)	163	(100.0%)
Race, n (%)						
Caucasian / White	142	(98.6%)	18	(94.7%)	160	(98.2%)
Black/African American	1	(0.7%)	0		1	(0.6%)
Asian /Oriental	1	(0.7%)	0		1	(0.6%)
Hispanic	0		1	(5.3%)	1	(0.6%)
Total	144	(100.0%)	19	(100.0%)	163	(100.0%)
Body weight at Screening (kg)						
n	144		19		163	
Mean (standard deviation)	75.69 (14.47)		76.13 (15.48)		75.74 (14.54)	
Median	75.00		73.00		75.00	
Range	45.0 - 130.0		45.0 - 104.0		45.0 - 130.0	
Height (cm)						
n	144		19		163	
Mean (standard deviation)	164.30 (10.31)		164.58 (11.52)		164.34 (10.42)	
Median	165.00		164.00		165.00	
Range	141.0 - 189.0		142.0 - 187.0		141.0 - 189.0	

The following table summarises baseline characteristics for the 144 non-randomized patients receiving VD (as well as those of the patients from Study MMY-3001 discussed above).

Table 5: Baseline Subject and Disease Characteristics of Study MMY-3001 and Study MMY-2045

(VELCADE Combination Efficacy Population)

		Velcade Combination Therapy			
	V Monotherapy	V + DOXIL	VD	Combined	Total
Subject Characteristics	N=322	N=324	N=144	N=468	N=790
Age (years)					
<65/≥65 (%)	60/40	63/37	50/50	59/41	59/41
Median (range) in years	62 (34; 88)	61 (28; 85)	65 (41; 86)	62 (28; 86)	62 (28; 88)
Sex: Male/Female (%)	54/46	58/42	54/46	57/43	56/44
Race: White/Other (%)	94/6	90/10	99/1	92/8	93/7

ECOG performance status[a]	N=321	N=323	N=143	N=466	N=787
0/1/≥2 (%)	45/55/0	43/57/0	18/60/22	35/58/7	39/57/4
Medical History					
Time since initial diagnosis	N=318	N=321	N=143	N=464	N=782
Median (range) in months	38 (3; 244)	35 (2; 185)	32 (2; 134)	35 (2; 185)	36 (2; 244)
Number of lines of prior therapy	N=322	N=334	N=144	N=468	N=790
1/>1 (%)	34/66	34/66	99/1	54/46	46/54
Prior stem cell transplant					
No. subjects (%)	173 (54)	186 (57)	59 (41)	245 (52)	418 (53)
Disease Characteristics					
Serum M-protein (g/dL)	N=321	N=322	N=140	N=462	N=783
Median (range)	2.7 (0; 10.3)	2.5 (0; 9.5)	2.4 (0; 32.0)	2.5 (0; 32.0)	2.6 (0; 32.0)
	N=318	N=318	N=122	N=440	N=758
Urine M-protein (mg/24 hours)	67	113	105	108	100
Median (Range)	(0; 39657)	(0; 24883)	(0; 32160)	(0; 32160)	(0; 39657)
% Plasma cells[b]	N=309	N=308	N=125	N=433	N=742
Median (Range)	35 (0; 100)	34 (0; 100)	30 (0; 100)	32 (0; 100)	33 (0; 100)
Cellularity[c]	N=297	N=297	N=99	N=396	N=693
Hyper-/Normo-/Hypocellular (%)	26/53/21	32/47/21	38/41/22	33/46/21	30/49/21
Presence of lytic bone lesions	N=317	N=318	N=136	N=454	N=771
Yes/No (%)	72/28	70/30	73/27	71/29	72/28
Presence of extramedullary plasmacytomas	N=322	N=324	N=142	N=466	N=788
Yes/No (%)	7/93	6/94	4/96	5/95	6/94

V=VELCADE; D=dexamethasone; ECOG=Eastern Cooperative Oncology Group

[a] For Study MMY-2045, the Karnofsky performance status was mapped to ECOG performance score.

[b] Based on combined results from bone marrow biopsy and aspirate. If both results are available, the maximal result is reported.

[c] Based on combined results from bone marrow biopsy and aspirate. If both results are available, the result from bone marrow biopsy is reported.

Note: Combined=V+DOXIL plus VD

Note: Percentages are calculated with the number of subjects in each group as denominator.

Note: Only the non-randomized VD subjects are included for Study VEL-MMY-2045.

Numbers analysed

Of the 190 subjects screened, 163 subjects [85.8% mITT] were enrolled and treated and 27 subjects [14.2%] were not treated.

Of 163 subjects treated, 77 subjects (47.2%) completed 8 cycles of treatment according to the drug administration data (at least 1 dose administrated in each cycle) and 86 subjects (52.8%) terminated before Cycle 8: 40 subjects [24.5%] due to drug-related AEs, 15 subjects [9.2%] due to PD, 9 subjects [5.5%] withdrew consent, 8 subjects [4.9%] due to death, 6 subjects [3.7%] due to “other” [not specified] reasons, 4 subjects [2.5%] due to investigator decision, 2 subjects [1.2%] due to CR/ PR, 1 subject [0.6%] due to SD with no randomization criteria, and 1 subject [0.6%], due to protocol violation.

Of the 86 subjects who terminated before Cycle 8, 82 subjects were in the non-randomized cohort, and 4 subjects were in the randomized cohort.

The mean duration (± standard deviation) of the study was 19.4 months (± 10.8) and the mean duration of follow-up was 15.4 months (± 10.0). The longest mean duration of the study was observed in the VDC arm (24.3 ± 12.6 months) as well as regards the follow-up (19.2 ± 11.9 months).

Outcomes and estimation

Primary endpoint

Results of the primary endpoint ORR in the mITT population are presented in the table below. Similar results were observed for the PP population.

Table 6: Summary of overall response rate (Study MMY-2045: mITT population)

		Non-randomized	Randomized	Total
		VD	VD, VDC, VDL	
		N=144	N=19	N=163
Overall best response[a]	E	123	19	142
	ORR (CR, VGPR, PR), n (%)	101 (70.1)	6 (31.6)	107 (65.6)
	[95% CI]	[62.0, 77.5]	[12.6, 56.6]	[57.8, 72.9]
	CR, n (%)	13 (9.0)	0 (0.0)	13 (8.0)
	VGPR, n (%)	48 (33.3)	0 (0.0)	48 (29.4)
	PR, n (%)	40 (27.8)	6 (31.6)	46 (28.2)
	SD, n (%)	17 (11.8)	12 (63.2)	29 (17.8)
	PD, n (%)	5 (3.5)	1 (5.3)	6 (3.7)
	Relapse from CR, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Overall best response is the best confirmed response recorded during study and before the start of subsequent therapies for multiple myeloma. Follow-up assessments are taken into consideration in calculations of Overall best confirmed response. Percentages are calculated on the total number of subjects.

Secondary endpoints

Results of secondary endpoints are presented in the table below.

Table 7: Efficacy results (Study MMY-2045: mITT population)

		Non-randomized VD	Randomized VD, VDC, VDL	Total
		(N=144)	(N=19)	(N=163)
Overall best response[a]				
Overall response rate[a]	ORR, n (%)	101 (70.1)	6 (31.6)	107 (65.6)
	[95% CI]	[62.0, 77.5]	[12.6, 56.6]	[57.8, 72.9]
Time to first response	Median days	43.0	Not estimable[b]	50.0
	[95% CI]	[43.0, 58.0]	Not estimable[b]	[43.0, 64.0]
Time to best response	Median days	78.0	Not estimable[b]	85.0
	[95% CI]	[64.0, 88.0]	Not estimable[b]	[75.0, 105.0]
Duration of response	Median days	345.0	156.0	295.0
	[95% CI]	[246.0, 433.0]	[91.0, 259.0]	[246.0, 416.0]
Time to progression	Median days	366.0	214.0	288.0
	[95% CI]	[281.0, 475.0]	[198.0, 234.0]	[235.0, 406.0]
Progression free survival	Median days	311.0	214.0	261.0
	[95% CI]	[224.0, 424.0]	[198.0, 234.0]	[219.0, 361.0]
One-year survival[c]	Estimate, %	80.2	89.0	81.2
	[95% CI]	[73.4, 86.9]	[62.4, 97.1]	[75.0, 87.4]

[a] Overall response rates were calculated using the best response (CR, VGPR, PR) during the study and before the start of subsequent therapies for multiple myeloma i.e., follow-up assessments were taken into consideration.

[b] Not estimable due to the low number of responders

[c] The proportion of subjects with a one year survival since the start of treatment in the randomized cohort, non-randomized cohort and across all cohorts.

Abbreviations: CI = confidence intervals, CR = complete response, ITT = modified intent-to-treat, N = total number of subject in cohort(s), ORR = overall response rate, PR = partial response, VGPR = very good partial response, VD = VELCADE + dexamethasone, VDC = VELCADE + dexamethasone + cyclophosphamide, VDL = VELCADE + dexamethasone + lenalidomide.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8: Summary of Efficacy for trial MMY-3001

Title: A Randomized Controlled Study of DOXIL®/CAELYX® (doxorubicin HCl liposome injection) and VELCADE® (bortezomib) or VELCADE Monotherapy for the Treatment of Relapsed Multiple Myeloma
Protocol DOXIL-MMY-3001
Randomized, parallel-group, open-label, multicenter study conducted in men and women 18 years of age or older who had relapsed/progressive or refractory multiple myeloma and who had received at least 1 prior line of therapy. Subjects were randomized in a 1:1 ratio to receive either VELCADE monotherapy or VELCADE plus DOXIL/CAELYX for up to 8 (21-day) cycles (more cycles could be given if it was considered that continued treatment would be beneficial) and were subsequently followed for survival. One interim analysis was prospectively defined after approximately 230 events (progression or death due to progression) were observed; the final analysis was to be done after approximately 460 events. Responses and progressions were assessed objectively by a computer algorithm based on the EBMT

criteria.		
Duration of main phase: Duration of run-in phase: Duration of extension phase:		Up to 8 (21-day) cycles Not applicable Follow-up for overall survival to continue for 5 to 7 years after enrollment of the last subject
Superiority		
Group A		VELCADE, 1.3 mg/m^2 IV, on Days 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles; n=322 randomized
Group B		VELCADE, 1.3 mg/m^2 IV, on Days 1, 4, 8, and 11 plus DOXIL/CAELYX 30 mg/m^2 IV, on Day 4 (following VELCADE administration) of each 21-day cycle for up to 8 cycles; n=324 randomized
Primary endpoint	TTP	Time to progression; the interval between the date of randomization and the date of disease progression (including relapse after CR) or death due to disease progression
Secondary	OS	Overall survival; the interval between the date of randomization and death from any cause
Secondary	ORR	The proportion of subjects who achieved a CR or PR
Other	PFS	Progression-free survival; the time from randomization until disease progression or death due to any cause
Other	TTR	Time to response; the time period from the randomization date to the first evaluation at which a subject had a durable response
Other	DoR	Duration of response; the time period from the first evaluation at which a subject had a durable response to the date of disease progression or death due to any cause
15 August 2006 for the primary analysis, and 6 February 2007 for the safety and survival update		

Results and analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat, response-evaluable, responders Clinical cutoff in 28 April 2006		
Descriptive statistics and estimate variability	Treatment group	VELCADE	Vc+DOX
	Number of subjects	n=322	n=324
	TTP (median days)	197.0	282.0
	95% CI	(170.0, 217.0)	(250.0, 338.0)
	Number of subjects	n=322	n=324
	OS No. died (%) (median days)	 39 (12.1) NA	 28 (8.6) NA
	95% CI	(NA, NA)	(NA, NA)

	Number of subjects	n=310	n=303
	ORR (CR+PR) n (%)	133 (43)	144 (48)
	95% CI	(37.3, 48.6)	(41.8, 53.3)
	Number of subjects	n=322	n=324
	PFS (median days)	222.0	340.0
	95% CI	(199.0, 248.0)	(295.0, NA)
	Number of subjects	n=133	n=144
	TTR (median days)	43.0	43.0
	range	(15, 197)	(21, 156)
	Number of subjects	n=133	n=144
	DoR (median days)	213.0	311.0
	95% CI	(180.0, 254.0)	(309.0, 394.0)
Effect estimate per comparison	Primary endpoint: TTP	Comparison groups	VELCADE vs. Vc+DOXIL
		hazard ratio	1.82
		95% CI	(1.41, 2.35)
		P-value	0.000004
	Secondary endpoint: OS	Comparison groups	VELCADE vs. Vc+DOXIL
		hazard ratio	1.48
		95% CI	(0.91, 2.41)
		P-value	0.113
	Secondary endpoint: ORR	Comparison groups	VELCADE vs. Vc+DOXIL
		P-value	0.2514
	Other endpoint: PFS	Comparison groups	VELCADE vs. Vc+DOXIL
		hazard ratio	1.67
		95% CI	1.30, 2.14
		P-value	0.000038
	Other endpoint: TTR	Comparison groups	VELCADE vs. Vc+DOXIL
		NA	NA
	Other endpoint: DoR	Comparison groups	VELCADE vs. Vc+DOXIL
		NA	NA
Notes	A hazard ratio >1 indicates an advantage for Vc+DOXIL At the time of the analysis, median OS was not achieved.		
Analysis description	**Updated survival analysis**		
Analysis population and time point description	Intent to treat Clinical cutoff in 28 November 2006		

Descriptive statistics and estimate variability	Treatment group	VELCADE	Vc+DOX
	Number of subjects	n=322	n=324
	OS No. died (%) (median days)	 81 (25.2) NA	 58 (17.9) NA
	95% CI	(551.0, NA)	(NA, NA)
	Effect estimate	hazard ratio	1.406
		95% CI	(1.002, 1.972)
		P-value	0.0476
Notes	Median OS was not achieved by the time of the updated analysis.		

CR=complete response; DoR=duration of response; DOX=DOXIL/CAELYX; EBMT=European Group for Blood and Marrow Transplantation; EORTC=European Organization for Research and Treatment of Cancer; IV= intravenously; NA=not available; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; TTP=time to progression; TTR=time to response; Vc=VELCADE; vs=versus

Table 9: Summary of Efficacy for trial MMY-2045

Title: A Phase 2, Multicenter, Randomized, Open-Label, Parallel Group Study to Evaluate the Safety and Efficacy of VELCADE® in Combination With Dexamethasone or VELCADE® in Combination With Dexamethasone and Cyclophosphamide or VELCADE® in Combination With Dexamethasone and Lenalidomide in Subjects With Multiple Myeloma Who are Refractory to or Have Relapsed / Progressed After Primary Therapy for Multiple Myeloma and Have Achieved Stable Disease After 4 Cycles of VELCADE® / Dexamethasone Therapy		
Study identifier	26866138-MMY-2045	
Design	Randomized, open-label, international, multicenter, Phase 2 study of adult men and women subjects, who were refractory to or had relapsed or progressed after their primary therapy for multiple myeloma. All enrolled subjects initially received up to 4 cycles of VELCADE plus dexamethasone (VD). Following non-randomized treatment period, subjects who achieved a complete response (CR), very good partial response (VGPR), or partial response (PR) continued to receive VD for a maximum of 4 additional cycles. Subjects with stable disease were randomized to receive up to 4 additional cycles of treatment with either VD, VD plus cyclophosphamide (VDC) or VD plus lenalidomide (VDL). Subjects with progressive disease (PD) were taken off study treatment. Treated subjects were followed-up for relapse and survival status.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	24 weeks (non-randomized + randomized treatment) Not Applicable (NA) 1 year post last dose/last subject
Hypothesis	Exploratory: No hypothesis stated	

Treatment groups	VD (non-randomized)		VELCADE 1.3 mg/m^2 IV on Day 1, 4, 8, 11 plus dexamethasone 20 mg orally daily, on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle. Up to 8, 21-day cycles. N=144
	VD (randomized)		VD as described for four, 21-day cycles (non-randomized treatment), followed by VD as described for 4 additional, 21-day cycles (randomized treatment). N=7
	VDC (randomized)		VD as described for four, 21-day cycles (non-randomized treatment), followed by VD as described plus cyclophosphamide 500 mg orally on Days 1, 8, and 15 for 4 additional, 21-day cycles (randomized treatment). N=8
	VDL (randomized)		VD as described for four, 21-day cycles (non-randomized treatment), followed by VD as described plus lenolidomide 10 mg orally on Days 1 through 14 for 4 additional, 21-day cycles (randomized treatment). N=4
Endpoints and definitions	Primary endpoint	ORR	Overall response rate. Subjects with CR, VGPR and PR during study and before the start of further therapies for multiple myeloma according to the International Myeloma Working Group (IMWG) criteria.
	Secondary endpoint	TTR	Time to response. Time from start of treatment to the date of the first documentation of a confirmed response.
	Secondary endpoint	DOR	Duration of response. Applied to subjects achieving at least PR by the IMWG criteria. Time from the start of at least PR (first observation of PR before confirmation) to the time of disease progression or relapse from CR, with deaths owing to causes other than progression not counted, but censored.
	Secondary endpoint	TTP	Time to progression. Time from start of treatment to the date of the first observation of disease progression or relapse from CR. Deaths owing to causes other than progression were not counted, but censored.
	Secondary endpoint	PFS	Progression-free survival. Time from start of treatment to date of disease progression, relapse from CR or death.
	Secondary endpoint	OS	Overall survival. Time from start of treatment to the date of death due to any cause.
	Secondary endpoint	1-year survival	The proportion of subjects alive one year after start of treatment (based on the Kaplan-Meier estimation).
Database lock	21 September 2011		
Results and analysis			

Analysis description	**Primary analysis**		
Analysis population and time point description	Modified ITT End of the follow-up period		
Descriptive statistics and estimate variability	Treatment group	VD (nonrandomized)	VD, VDC, VDL (randomized)
	Number of subjects	144	19
	ORR n (%)	101 (70.1)	6 (31.6)
	95% CI	[62.0, 77.5]	[12.6, 56.6]
	TTR median days	43.0	NE
	95% CI	[43.0, 58.0]	[152.0, NE]
	DOR median days	345.0	156.0
	95% CI	[246.0, 433.0]	[91.0, 259.0]
	TTP median days	366.0	214.0
	95% CI	[281.0, 475.0]	[198.0, 234.0]
	PFS median days	311.0	214.0
	95% CI	[224.0, 424.0]	[198.0, 234.0]
	OS median days	NE	NE
	95% CI	[888.0, NE]	[982.0, NE]
	1-year survival estimate %	80.2	89.0
	95% CI	[73.4, 86.9]	[62.4, 97.1]
Effect estimate per comparison	Not applicable		
Notes	Due to the extremely small number of randomized subjects, planned outputs with a breakdown into randomization groups were omitted for descriptive or categorical statistics other than for general subject population overviews and were replaced by a general “randomized subjects” cohort combining the 3 randomization arms.		

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

In order to provide further evidence in support of the benefit of VELCADE in combination with dexamethasone in relapsed or refractory multiple myeloma, the MAH has performed a matched pair analysis in which the outcomes of subjects in the VELCADE-dexamethasone group from Study MMY-2045 were compared to the outcomes of a systematically matched control group of subjects from the

VELCADE monotherapy groups of the APEX study (Study M34101-039, Phase III study of bortezomib compared with high dose dexamethasone for patients with relapsed myeloma (1 to 3 prior therapies) submitted at the time of initial marketing authorisation) and of Study MMY-3001.

The MAH conducted sensitivity analysis including 8 variables that were identified from a review of the literature as being related to clinical outcome in the matching algorithm: age, Eastern Cooperative Oncology Group (ECOG) score, type of myeloma, percent of plasma cells, prior dexamethasone, hemoglobin, creatinine clearance, and albumin.

Using this matching algorithm, 127 pairs were identified, corresponding to approximately 90% of the 142 subjects from Study MMY-2045.

Most of the baseline prognostic factors included in this sensitivity analysis were well balanced within the 127 matched pairs. Some imbalance was noted for age, ECOG score, and type of myeloma, with the imbalance favouring the VELCADE monotherapy group in each case.

At baseline, 42.5% of subjects had >30% plasma cells present in the bone marrow aspirate or biopsy, 23.2% had a creatinine clearance of <50 mL/min, and 70.5% had prior exposure to dexamethasone. The median baseline hemoglobin was 111.0 g/L; albumin was 3.9 g/dL.

Overall Response Rate

The odds ratio (95% CI) of achieving a response for VELCADE plus dexamethasone versus VELCADE monotherapy was 3.769 (2.045, 6.947); p<0.001 (Table 10).

Table 10: Best Overall Response Rate – All Matched Pairs analysis set

	Vc Monotherapy	Vc + Dex	OR[a](95% CI)	P-value[b]
Analysis set: all matched pairs	127	127		
Response category[c]				
CR	11 (8.7%)	11 (8.7%)		
PR	46 (36.2%)	82 (64.6%)		
ORR (CR, PR)	57 (44.9%)	93 (73.2%)	3.769 (2.045, 6.947)	<.001
SD	53 (41.7%)	13 (10.2%)		
PD	11 (8.7%)	3 (2.4%)		
NE	6 (4.7%)	18 (14.2%)		

Key: Vc=VELCADE; Dex=dexamethasone; CR=Complete Response; PR=Partial Response; ORR=Overall response rate; SD=Stable disease; PD=Progressive Disease; NE=Not evaluable; OR=odds ratio.
[a] Mantel-Haenszel estimate of the odds ratio, stratified by matched pair, for Vc + Dex vs. Vc monotherapy is provided.
An odds ratio > 1 indicates an advantage for Vc + Dex.
[b] P-value is from the Cochran Mantel-Haenszel Chi-Square test, stratified by matched pair.
[c] Response in Study MMY2045 (Vc + Dex group) was determined by IDMC using the IMWG criteria; response in Studies DOXIL-MMY3001 and M34101-039 (Vc monotherapy group) was derived using programmed algorithm based on the EBMT criteria.

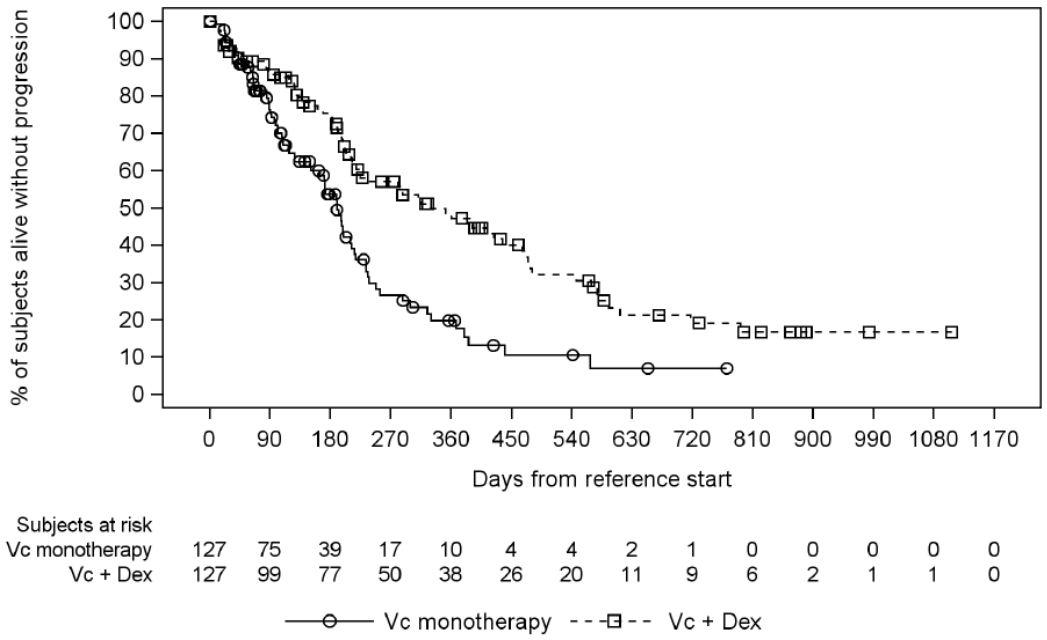
Progression-free Survival

After a median follow up of 15.1 months (460 days) in the VELCADE plus dexamethasone group and 9.5 months (289 days) in the VELCADE monotherapy group, the median PFS was 10.7 months (327 days) and 6.2 months (190 days) for the VELCADE plus dexamethasone and VELCADE monotherapy groups, respectively. The HR (95% CI) for VELCADE plus dexamethasone versus VELCADE monotherapy was 0.511 (0.309, 0.845); p=0.008 (Table 11, Figure 2).

Table 11: Progression-free survival – All Matched Pairs analysis set

	Vc Monotherapy	Vc + Dex
Analysis set: all matched pairs	127	127
Descriptive[a]		
Time to disease progression/death (days)		
Number of assessed	127	127
Number of censored (%)	53 (41.7%)	55 (43.3%)
Number of events (%)	74 (58.3%)	72 (56.7%)
25% quantile (95% CI)	92.0 (66.0; 110.0)	182.0 (126.0; 200.0)
Median (95% CI)	190.0 (151.0; 212.0)	327.0 (224.0; 467.0)
75% quantile (95% CI)	299.0 (233.0; 386.0)	595.0 (478.0;NE)
P-value[b]		0.008
Hazard ratio (95% CI)[c]		0.511 (0.309; 0.845)

Key: Vc = VELCADE; Dex = dexamethasone; CI = confidence interval; NE = not estimable.
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on log-rank test stratified by matched pair.
[c] Hazard ratio estimate for Vc + Dex vs. Vc monotherapy is based on a Cox regression model, stratified by matched pair.
A hazard ratio < 1 indicates an advantage for Vc + Dex.



Key: Vc = VELCADE; Dex = Dexamethasone;
Reference start date is the date of randomization for randomized studies; otherwise the date of first dose is used.

Figure 2 - Progression-free survival – All Matched Pairs analysis set

Time to Progression

The median time to progression (TTP) was 12.9 months (392 days) for the VELCADE plus dexamethasone group compared with 6.4 months (196 days) in the VELCADE monotherapy group. The HR (95% CI) for VELCADE plus dexamethasone versus VELCADE monotherapy was 0.385 (0.212, 0.698); p=0.001 (Table 12).

Table 12: Time to Disease Progression – All Matched Pairs analysis set

	Vc Monotherapy	Vc + Dex
Analysis set: all matched pairs	127	127
Descriptive[a]		
Time to disease progression (days)		
Number of assessed	127	127
Number of censored (%)	59 (46.5%)	66 (52.0%)
Number of events (%)	68 (53.5%)	61 (48.0%)
25% quantile (95% CI)	97.0 (66.0; 127.0)	199.0 (161.0; 219.0)
Median (95% CI)	196.0 (172.0; 218.0)	392.0 (288.0; 478.0)
75% quantile (95% CI)	325.0 (233.0; 386.0)	612.0 (547.0;NE)
P-value[b]		0.001
Hazard ratio (95% CI)[c]		0.385 (0.212; 0.698)

Key: Vc = VELCADE; Dex = dexamethasone; CI = confidence interval; NE = not estimable.
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on log-rank test stratified by matched pair.
[c] Hazard ratio estimate for Vc + Dex vs. Vc monotherapy is based on a Cox regression model, stratified by matched pair.
A hazard ratio < 1 indicates an advantage for Vc + Dex.

Overall Survival

After a median follow up of 26.8 months (817 days) in the VELCADE plus dexamethasone group and 17.7 months (539 days) in the VELCADE monotherapy group, the overall survival OS data were not yet mature, and the median OS was not reached in either group (Table 13).

Table 13: Overall survival – All Matched Pairs analysis set

	Vc Monotherapy	Vc + Dex
Analysis set: all matched pairs	127	127
Descriptive[a]		
Overall survival (days)		
Number of assessed	127	127
Number of censored (%)	87 (68.5%)	84 (66.1%)
Number of events (%)	40 (31.5%)	43 (33.9%)
25% quantile (95% CI)	426.0 (335.0; 499.0)	554.0 (266.0; 785.0)
Median (95% CI)	NE (668.0;NE)	NE (850.0;NE)
75% quantile (95% CI)	NE (NE ;NE)	NE (NE ;NE)
1 year survival rate % (95% CI)	80.4 (71.9; 86.5)	79.3 (70.9; 85.5)
2 year survival rate % (95% CI)	54.7 (42.3; 65.4)	69.6 (60.2; 77.3)
P-value[b]		0.796
Hazard ratio (95% CI)[c]		0.936 (0.564; 1.552)

Key: Vc = VELCADE; Dex = dexamethasone; CI = confidence interval; NE = not estimable.
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on log-rank test stratified by matched pair.
[c] Hazard ratio estimate for Vc + Dex vs. Vc monotherapy is based on a Cox regression model, stratified by matched pair.
A hazard ratio < 1 indicates an advantage for Vc + Dex.

Supportive study MMY-3021 for the combination with dexamethasone

Methods

Study MMY-3021 was a randomized, open-label, Phase 3, non-inferiority study that compared the safety and efficacy of VELCADE administered by either the IV and SC route in 222 subjects with progressive disease who had received 1 to 3 prior lines of therapy (previous treatment with Velcade was an exclusion criterion) and had measurable disease and evidence of disease progression since their last previous therapy for multiple myeloma.

Subjects were adults with Karnofsky performance scores ≥70% and no prior Velcade exposure. Subjects were eligible to participate whether they had received or did not receive a prior stem cell transplant; at baseline 23% (51 patients) of total subjects had stem cell transplantation.

They were randomized in a 2:1 (SC:IV) ratio to receive either SC or IV Velcade 1.3 mg/m^2 on Days 1, 4, 8, and 11 of each 3 week cycle. Dexamethasone 20 mg orally on the day of and day after each Velcade dose could be added for subjects who had no change or a PR, but had not progressed, after 4 cycles of treatment with Velcade monotherapy.

The primary endpoint was to compare the ORR, defined as the proportion of subjects with CR or PR after 4 cycles of VELCADE SC and IV. Non-inferiority was defined as retaining 60% of the IV (active control) treatment effect as measured by ORR.

Secondary endpoints considered in the present variation were CR, near complete response (nCR), and very good partial response (VGPR) rates after 4 cycles of single-agent VELCADE, the ORR after 8 cycles including the effect of adding dexamethasone, the duration of response, TTP, PFS, 1-year survival, and time to response following VELCADE treatment, administered either SC or IV.

Under the alternative hypothesis where the ORRs are both assumed to be 35.5%, which is the lower limit of the 95% confidence interval (CI) of the pooled response rate, and assuming a 1-sided alpha level of 0.025 and approximately 80% power, approximately 216 subjects (144 in the SC treatment group and 72 in the IV treatment group) were needed to show non-inferiority of SC to IV VELCADE.

Results

147 subjects in the SC treatment group and 74 subjects in the IV treatment group were included in the safety analysis dataset. 121 subjects received Velcade-Dexamethasone (82 in the SC arm and 39 in the IV arm), and 32 subjects received Velcade monotherapy during the period after Cycle 4 when dexamethasone was allowed. Both groups of subjects received a median of 8 cycles of Velcade.

The following parameters were similar in the Velcade monotherapy and Velcade-Dexamethasone arms, respectively:

- Median time on study: 22.86 weeks vs 22.71 weeks
- Median VELCADE dose intensity (Cycles 1 to 4): 5.20 mg/m^2/cycle vs 5.13 mg/m^2/cycle
- Median VELCADE dose intensity (Cycles ≥5): 4.80 mg/m^2/cycle vs 4.88 mg/m^2/cycle
- Median VELCADE relative dose intensity (Cycles 1 to 4): 1.00 mg/m^2/cycle vs 0.99 mg/m^2/cycle
- Median VELCADE relative dose intensity (Cycles ≥5): 0.92 mg/m^2/cycle vs 0.94 mg/m^2/cycle

The median dose intensity of dexamethasone in the Velcade-Dexamethasone group was 160 mg/cycle.

Thirty-five (16%) subjects discontinued treatment due to disease progression. Forty-nine (22%) subjects discontinued due to an adverse event, 39 (18%) subjects discontinued due to a drug-related adverse event.

Results presented here focus on the period after cycle 4 when dexamethasone was permitted to be added to Velcade.

Table 14: Cross-Tabulation of Summary of Best Response after 4 cycles vs. after 8 cycles by dexamethasone exposure

(Study 26866138-MMY-3021: Response-Evaluable Subjects With Cycle 5 Exposure Analysis Set)
Dexamethasone Exposure: Yes

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

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Cross reference: (bortezomib\0020\Mod5.3.5.1\MMY-3021\Table34)

Comparing the response before (Velcade monotherapy) and after (Velcade-Dexamethasone) cycle 4, the addition of dexamethasone from Cycle 5 onward improved the ORR (CR+PR) from 42% at the end of Cycle 4 to 52% at the end of Cycle 8.

Compared with the responses seen after 4 cycles of Velcade monotherapy, for subjects who received treatment with additional dexamethasone, 30% of subjects (in both SC and IV arms) who were initially non-responders improved to a PR, and 13% of subjects (in both SC and IV arms) with a PR improved to a CR.

For the 121 subjects who received additional dexamethasone after Cycle 4, the following time to event endpoints were observed: TTP (median 10.4 months [316 days]), PFS (10.2 months [310 days]), and 1-year survival rate (86%). The results for these endpoints in the subgroup of 101 subjects in the Velcade monotherapy group were 7.3 months (221 days), 6.2 months (189 days), and 58.9%, respectively.

2.4.2. Discussion on clinical efficacy

Study MMY-3001, designed to compare the most active treatment (Velcade) vs the combination (Velcade-Caelyx), is considered adequate to support the proposed indication of Velcade in combination with pegylated liposomal-doxorubicin 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 same indication was already approved in 2007 for Caelyx.

Final survival data for study MMY-3001 will be available at the end of 2013 when the protocol-required events (517 deaths) are expected. The CHMP recommended that results of the long-term follow-up and survival analysis of study MMY-3001 be submitted when available.

The MAH also proposed to extend the indication to treatment of patients with relapsed multiple myeloma which would allow the possibility of early treatment in patients with only relapse, but no

further progression. This was not considered acceptable as not supported by data. In addition, the MAH also proposed to remove the restriction to "*patients who have already undergone or are unsuitable for bone marrow transplantation"* on the basis of the inclusion of subjects who had either received or had not received a prior bone marrow transplant into Studies MMY-3001, MMY-2045, and MMY-3021. This was not agreed since no formal analysis was performed to demonstrate the effect of Velcade-Caelyx in the general patient population independently of a prior bone marrow transplant. During the assessment, the MAH did no longer pursue with these proposed changes.

Study MMY-2045 was also submitted to support the use of Velcade in combination with dexamethasone. Due to the non-comparative design of the study, the assessment of the efficacy of the combination Velcade-Dexamethasone has intrinsic limitations.

The combination Velcade-Dexamethasone obtained an ORR (CR, VGPR, PR) of 65.6% across all cohorts and 70.1% in the non-randomized Velcade-Dexamethasone cohort. These are substantially higher response rates compared to the Velcade monotherapy group of Study MMY-3001 (43%), and to the previous, controlled Velcade monotherapy (APEX) study (38%).

In the Velcade-Dexamethasone group of Study MMY-2045, the median TTP (12.0 months), PFS (10.2 months), and duration of overall response (11.3 months) extended beyond the median treatment period of 4.8 months even if a high number of censored were recorded (50% and 41%, respectively). These results appear significantly better than in Study MMY-3001 or APEX.

However, in view of the different study designs and study populations of these studies, such comparisons are not completely appropriate. In fact, in study MMY-2045, 99% of subjects had received just one prior line of therapy for MM and 41% had undergone stem cell transplant. In study MMY-3001, 66% of subjects had received more than one prior line of therapy for MM and 54% had undergone stem cell transplant. In the APEX trial 60% of subjects had received more than one prior line of therapy for MM and 67% had undergone stem cell transplant.

Direct assessment of the possible beneficial effect of bortezomib + dexamethasone compared to bortezomib alone from the results of the study MMY-2045 is not possible, as this was not the objective of the study.

Results from Study MMY-3021 are consistent with a higher efficacy of the combination relative to Velcade monotherapy but can only be considered supportive. While the ORR after 8 cycles (including the effect of adding dexamethasone) was one of the secondary objectives of the study, the direct assessment of the possibly beneficial effect of bortezomib + dexamethasone vs. bortezomib alone from the results of the study MMY-3021 was not possible. The reason is that the addition of dexamethasone was only possible after cycle 4. Although the addition of dexamethasone from cycle 5 onward improved the ORR, this improvement of ORR could also attribute to the increased number of bortezomib cycles.

In order to provide further evidence in support of the benefit of VELCADE in combination with dexamethasone, the MAH has performed matched pair analyses in which the outcomes of subjects in the VELCADE-dexamethasone group from Study MMY-2045 were compared to the outcomes of a systematically matched control group of subjects from the VELCADE monotherapy groups of the APEX study and of Study MMY-3001. The analysis conducted with 127 pairs selected based on appropriate covariates showed PFS results favouring the Velcade-dexamethasone treatment group [10.7 vs 6.2 months HR: 0.511(0.309-0.845) p=0.008]. Similar results favouring the Velcade-dexamethasone combination were also observed for the other endpoints that were evaluated.

2.4.3. Conclusions on the clinical efficacy

Data from study MMY-3001 are considered adequate to support the proposed indication of Velcade in combination with pegylated liposomal-doxorubicin.

Results of study MMY-2045 supported by those of study MMY-3021 as well as the matched pair analyses support the use of Velcade in combination with dexamethasone.

2.5. Clinical safety

The MAH presented integrated safety population data from Study MMY-3001 and Study MMY-2045. The report included data on 799 subjects, of whom 481 received Velcade combination therapy (318 Velcade-Caelyx and 163 Velcade-Dexamethasone) and 318 received Velcade monotherapy.

Safety data from Study MMY-3021 for subjects who received treatment beginning in Cycle 5 and beyond (i.e., when dexamethasone was allowed) were considered supportive and presented separately.

The integrated safety analyses were carried out on the safety population, which included all subjects who received at least 1 dose of any study drug. All data summaries are presented in 4 groups: Velcade monotherapy, Velcade-Caelyx, Velcade-Dexamethasone, and the combined Velcade combination therapy group (referred to as the "combined therapy group") that included subjects who received Velcade-Caelyx and those who received Velcade-Dexamethasone.

The safety data for Studies MMY-3001 and MMY-3021 are from the updated safety reports with clinical cutoff dates of 28 November 2006 and 26 February 2011, respectively. The safety data for Study MMY-2045 are from the final CSR with a clinical cutoff date of 2 August 2011.

At the time of clinical cutoff, almost all subjects (98%) from the key studies (MMY-3001 and MMY-2045) had discontinued from treatment. The most common reasons for treatment discontinuation were adverse events (30%), completion of 8 cycles of treatment (27%), and disease progression (20%). At the time of the long-term extension clinical cutoff for Study MMY-3021, all 221 treated subjects had either completed the study (155 subjects [70%]) or discontinued from treatment (66 subjects [30%]).

Patient exposure

Overall, 163 subjects in Study MMY-2045 were exposed to a total median (range) Velcade dose of 50.1 (2 to 92) mg or 26.2 (1 to 42) mg/m^2 during 8 cycles of treatment. The median duration (range) of exposure to Velcade was 145.0 (1 to 229) days over a median number (range) of 7 (1 to 8) cycles. Median (range) exposure to Velcade was 32.3 (2 to 46) mg or 18.4 (1 to 21) mg/m^2 during Cycles 1 to 4, and 26.4 (0 to 46) mg or 14.6 (1 to 21) mg/m^2) during Cycles 5 to 8. A total of 163 subjects were exposed to a total median (range) dexamethasone dose of 900.0 (20 to 1300) mg. Seven subjects were exposed to a total median (range) cyclophosphamide dose of 6000.0 (5000 to 6000) mg and four subjects were exposed to a total median (range) lenalidomide dose of 560 (450 to 560) mg.

A summary of patient exposure in Study MMY-3001 and Study MMY-2045 is presented in Table 15.

Table 15: Treatment Exposure: Overview; VELCADE Combination Integrated Analysis of Safety Safety Analysis Set

		Velcade Combination Therapy		
Exposure, median (range)	V Monotherapy[a]	V + DOXIL[a]	VD[b]	Combined[c]
	N=318	N=318	N=163	N=481
Total number of cycles received	6.0 (1; 18)	6.0 (1; 18)	7.0 (1; 8)	6.0 (1; 18)
Treatment duration, weeks	17.07 (0.1; 52.4)	18.50 (0.6; 57.1)	20.86 (0.1; 67.6)	19.57 (0.1; 67.6)
VELCADE	N=318	N=318	N=163	N=481
Dose intensity, mg/m^2/cycle	4.75 (1.3; 5.6)	4.67 (2.5; 5.4)	4.42 (1.3; 5.3)	4.59 (1.3; 5.4)
Relative dose intensity (%)	91.3 (24; 108)	89.7 (48; 104)	85.0 (24; 102)	88.2 (24; 104)
DOXIL/CAELYX	N=0	N=315	N=0	N=315
Dose intensity, mg/m^2/cycle	-	29.83 (17.7; 35.0)	-	29.83 (17.7; 35.0)
Relative dose intensity (%)	-	99.4 (59; 117)	-	99.4 (59; 117)
Dexamethasone	N=0	N=0	N=163	N=163
Dose intensity, mg/cycle	-	-	150.00 (20.0; 162.5)	150.00 (20.0; 162.5)
Relative dose intensity (%)	-	-	93.8 (13; 102)	93.8 (13; 102)

V=VELCADE; D=dexamethasone
[a] V Monotherapy and V+DOXIL data are from Study MMY-3001.
[b] VD data are from Study MMY-2045.
[c] Combined= V+DOXIL data plus VD data.
Note: Percentages are calculated with the number of subjects in each group as denominator.
Note: One subject in the Velcade Monotherapy group from Study MMY-3001 crossed over to receive DOXIL after Cycle 12; exposure data beyond Cycle 12 from this subject is not included.

Adverse events

An overall summary of treatment-emergent adverse events from the integrated safety population (Study MMY-3001 and Study MMY-2045) is presented in Table 16.

Table 16: Overview of Treatment-Emergent Adverse Events; VELCADE Combination Integrated Analysis of Safety; Safety Analysis Set

		Velcade Combination Therapy		
	V Monotherapy[a]	V + DOXIL[a]	VD[b]	Combined[c]
Analysis Set: Safety	318	318	163	481
Any TEAE	309 (97.2%)	316 (99.4%)	157 (96.3%)	473 (98.3%)
Drug-related	279 (87.7%)	308 (96.9%)	155 (95.1%)	463 (96.3%)
Any serious TEAE	105 (33.0%)	120 (37.7%)	61 (37.4%)	181 (37.6%)
Drug-related	51 (16.0%)	71 (22.3%)	40 (24.5%)	111 (23.1%)
Maximum severity of any TEAE				
Grade 1	16 (5.0%)	11 (3.5%)	8 (4.9%)	19 (4.0%)
Grade 2	73 (23.0%)	38 (11.9%)	35 (21.5%)	73 (15.2%)
Grade 3	150 (47.2%)	169 (53.1%)	73 (44.8%)	242 (50.3%)

		Velcade Combination Therapy		
	V Monotherapy[a]	V + DOXIL[a]	VD[b]	Combined[c]
Grade 4	69 (21.7%)	94 (29.6%)	19 (11.7%)	113 (23.5%)
Grade 5	1 (0.3%)	4 (1.3%)	11 (6.7%)	15 (3.1%)
Treatment discontinuation due to TEAE[d]	80 (25.2%)	110 (34.6%)	39 (23.9%)	149 (31.0%)
Drug-related[e]	73 (23.0%)	102 (32.1%)	33 (20.2%)	135 (28.1%)

V=Velcade; D=dexamethasone; AE=adverse event; TEAE=treatment-emergent adverse event

[a] Vc Monotherapy and Vc+DOXIL data are from Study MMY-3001.

[b] VD data are from Study MMY-2045.

[c] Combined= V+DOXIL data plus VD data.

[d] For subjects that were indicated as discontinued due to AE on the treatment termination case report form page, some of the corresponding AE numbers were not available in the AE dataset; some of the corresponding AEs were not treatment-emergent per definition. These subjects are not included here.

[e] Includes subjects who had at least one adverse event that led to treatment discontinuation and was considered related to study drug.

Note: Percentages are calculated with the number of subjects in each group as denominator.

Note: In Study MMY-2045, for adverse events where only a severity grade is reported, the severity grade is remapped to a National Cancer Institute Common Terminology Criteria for Adverse Events toxicity grade.

In general, the overall safety profile was similar between the combined therapy and Velcade monotherapy groups. However, 98% of subjects who received combination therapy experienced at least 1 treatment-emergent adverse event (TEAE).

The most frequently reported treatment-emergent adverse events occurred in the following system organ classes (combined therapy group versus Velcade monotherapy):

- Gastrointestinal Disorders (74% versus 73%): specifically, diarrhea (41% versus 39%), nausea (36% versus 40%, respectively), and constipation (31% in each group);
- Nervous System Disorders (72% versus 70%): specifically, peripheral neuropathy(19% versus 26%), neuralgia (17% versus 20%), and peripheral sensory neuropathy (15% versus 13%);
- General Disorders and Administrative Site Conditions (69% versus 62%): specifically, fatigue (32% versus 28%), pyrexia (25% versus 22%), and asthenia (22% versus 18%).

Peripheral oedema was reported in 17% of subjects in the Velcade+ Dexamethasone group and 5% of subjects in the Velcade monotherapy group.

Nervous System Disorders (particularly peripheral neuropathy) and Metabolism and Nutritional Disorders (particularly hyperglycemia and diabetes mellitus) are recognized treatment-limiting toxicities associated with the use of Velcade. Therefore, a separate examination of these specific types of adverse events of clinical interest was undertaken. Overall, 50% of subjects in the combined therapy group and 52% of subjects in the Velcade monotherapy group experienced a Peripheral Neuropathy adverse event; in 11% and 14% of subjects, respectively, the adverse events were considered as Grade 3 or higher.

The incidence of Metabolism and Nutritional Disorders, specifically, hyperglycemia and diabetes mellitus, was 5% in the combined therapy group 1% in the Velcade monotherapy group. The percentage of adverse events that were considered as Grade 3 or higher was <1% in each group.

Serious adverse event / deaths / other significant events

From the integrated safety population (Study MMY-3001 and Study MMY-2045) report, 56.5% of TEAEs in the Velcade-Dexamethasone group were of Grade 3-4 severity. This compares favourably with 68.9% in the Velcade monotherapy group.

The most frequently reported Grade 3 or higher treatment-emergent adverse events occurred in the Blood and Lymphatic System Disorders system organ class (42% for the combined therapy and 35% for the Velcade monotherapy groups). Specifically, these included adverse events of neutropenia (23% versus 16%, respectively), thrombocytopenia (22% versus 17%, respectively), and anemia (9% in each group).

Grade 3 or higher peripheral neuropathy was observed in 11% in the combined therapy group and 14% of subjects in the Velcade monotherapy group.

The percentage of Metabolism and Nutritional Disorders that were considered as Grade 3 or higher was <1% in each group.

The incidence of TEAEs leading to death (Grade 5) appeared to be somewhat higher with Velcade-Dexamethasone (6.7%) than with Velcade monotherapy (0.3%).

The overall incidence of death was similar between the combination therapy and Velcade monotherapy groups (23% versus 25%, respectively). The most common cause of death was progressive disease (13% versus 20%, respectively). However, in the in the Velcade-dexamethasone group there was a higher incidence of deaths due to adverse events (Table 17).

Table 17: Overall incidence and causes of death; VELCADE Combination Integrated Analysis of Safety; Safety Analysis Set

(VELCADE Combination Integrated Analysis of Safety)

		VELCADE Combination Therapy		
	VELCADE Monotherapy[a]	VELCADE + DOXIL[a]	Vc + Dex[b]	Combined[c]
Analysis Set: Safety	318	318	163	481
Total number of subjects who died	80 (25.2%)	57 (17.9%)	55 (33.7%)	112 (23.3%)
Death due to all causes	80 (25.2%)	57 (17.9%)	55 (33.7%)	112 (23.3%)
Progressive disease	63 (19.8%)	34 (10.7%)	27 (16.6%)	61 (12.7%)
Adverse event	9 (2.8%)	11 (3.5%)	15 (9.2%)	26 (5.4%)
Drug-related	5 (1.6%)	4 (1.3%)	4 (2.5%)	8 (1.7%)
Other	8 (2.5%)	12 (3.8%)	13 (8.0%)	25 (5.2%)
Death due to all causes within 30 days of last dose	14 (4.4%)	11 (3.5%)	12 (7.4%)	23 (4.8%)
Progressive disease	6 (1.9%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Adverse event	7 (2.2%)	10 (3.1%)	11 (6.7%)	21 (4.4%)
Drug-related	3 (0.9%)	4 (1.3%)	3 (1.8%)	7 (1.5%)
Other	1 (0.3%)	0	0	0

Vc=VELCADE; Dex=dexamethasone
Note: Percentages are calculated with the number of subjects in each group as denominator.
[a] Vc monotherapy and Vc+DOXIL data in these columns are from Study MMY-3001
[b] Vc+Dex data in this column are from Study MMY-2045
[c] Combined= Vc+DOXIL data plus Vc+Dex

The incidence of treatment-emergent adverse events that led to death was low and similar between the combined therapy (5%) and Velcade monotherapy (4%) groups. All occurred at an incidence of <2%. The most common adverse event that led to death was pneumonia (<1% in the combined therapy group and 1% in the Velcade monotherapy group).

Treatment-emergent adverse events that were considered drug related and led to death, occurred in 2% of the subjects in both the combined therapy and Velcade monotherapy groups. All adverse events occurred at an incidence of <1% (Table 18).

Table 18: Treatment-Emergent Drug-Related Adverse Events with outcome death by system organ class and preferred term; VELCADE Combination Integrated Analysis of Safety; Safety Analysis Set

		Vc Combination Therapy		
	Vc Monotherapy[a]	Vc + DOXIL[a]	Vc + Dex[b]	Combined[c]
Analysis Set: Safety	318	318	163	481
Total number of subjects with drug-related treatment-emergent adverse event with outcome death	6 (1.9%)	4 (1.3%)	4 (2.5%)	8 (1.7%)
MedDRA system organ class/Preferred term				
Cardiac disorders	0	1 (0.3%)	2 (1.2%)	3 (0.6%)
Cardiac arrest	0	1 (0.3%)	0	1 (0.2%)
Cardiac failure	0	0	1 (0.6%)	1 (0.2%)
Myocardial infarction	0	0	1 (0.6%)	1 (0.2%)
Infections and infestations	4 (1.3%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Neutropenic sepsis	0	1 (0.3%)	0	1 (0.2%)
Pneumonia	3 (0.9%)	1 (0.3%)	0	1 (0.2%)
Sepsis	0	0	1 (0.6%)	1 (0.2%)
Meningitis bacterial	1 (0.3%)	0	0	0
Renal and urinary disorders	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Oliguria	0	0	1 (0.6%)	1 (0.2%)
Renal failure acute	0	1 (0.3%)	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Acute respiratory distress syndrome	0	0	1 (0.6%)	1 (0.2%)
Pulmonary hypertension	0	1 (0.3%)	0	1 (0.2%)
Pulmonary fibrosis	1 (0.3%)	0	0	0
Metabolism and nutrition disorders	0	1 (0.3%)	0	1 (0.2%)
Tumour lysis syndrome	0	1 (0.3%)	0	1 (0.2%)
Vascular disorders	0	0	1 (0.6%)	1 (0.2%)
Hypotension	0	0	1 (0.6%)	1 (0.2%)
General disorders and administration site conditions	1 (0.3%)	0	0	0
Death	1 (0.3%)	0	0	0

[a] Vc monotherapy and Vc+DOXIL data in these columns are from Study MMY-3001
[b] Vc + Dex data in this column are from Study MMY-2045
[c] Combined= Vc+DOXIL data plus Vc+Dex

Laboratory findings

No significant hematologic or serum chemistry toxicities were identified with the use of the combination regimens. For most laboratory parameters, the percentage of subjects in the integrated analysis set who had hematologic or serum chemistry toxicities of Grade 0 to 2 at baseline that worsened to Grade 3-4 during treatment was similar between the combination therapy and VELCADE monotherapy groups.

Safety in special populations

To evaluate potential differences in the safety profiles of the Velcade combination regimens within special patient populations, adverse events were analyzed by subgroups of subjects defined by age (<65 versus ≥65), race (White versus non-White), and sex. The conclusion from this analysis was that the safety profiles within subgroups of subjects defined by age, race, and sex, were similar between the combined therapy and Velcade monotherapy groups and consistent with the overall study populations. Where there were differences between subjects who were ≥65 and <65 years old, these were consistent with previous Velcade experience.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction and other interactions have been reported.

Discontinuation due to adverse events

The percentage of subjects that experienced a treatment-emergent adverse event that resulted in a dose adjustment of any study drug was 45% in the combined therapy group and 31% in the Velcade monotherapy group. Most commonly this was for Nervous System Disorders (26% in the combined therapy group and 23% in the Velcade monotherapy group).

Peripheral neuropathy was the most common treatment-emergent adverse event that led to a permanent stop of any study drug in all treatment groups. In the Velcade-Dexamethasone group, 4% of subjects also had a permanent stop of study drug for polyneuropathy.

Palmar-plantar erythrodysaesthesia syndrome resulted in a permanent stop of study drug in 6% of subjects in the Velcade-DOXIL group; the only group with subjects who had a permanent stop of drug for this reason.

Supportive Safety data from Study MMY-3021

The safety database from Study MMY-3021 submitted to support the use of Velcade in combination with dexamethasone included 121 (55% out of 221) subjects who received dexamethasone add-on after Cycle 4 (82 in the SC arm and 39 in the IV arm) and 32 received Velcade single agent. Patients who were allowed to be given dexamethasone after cycle 4 had no change or a PR and were without progression disease.

After cycle 4, the safety profile was similar between the treatment groups (also including Grade 3 or higher AEs), with the exception of serious treatment-emergent adverse events being higher in Vc+Dex group (16% [19 of 121 subjects]) than in the VELCADE monotherapy group (6% [2 of 32 subjects]).

The higher incidence of serious adverse events in the Vc+Dex group was primarily due to pneumonia (in 6 of 121 subjects, 5%). Other most frequently reported Grade 3 or higher adverse events in the Vc+Dex and the VELCADE monotherapy groups, respectively, were neutropenia (3% versus 13%) and anemia (5% versus 0%). All other treatment-emergent serious adverse events occurred at an incidence of 3% or less.

Table 19: Overview of Treatment-Emergent Adverse Events in Cycles 5-10 (new onsets) by dexamethasone exposure

(VELCADE Combination Integrated Analysis of Safety: Safety Subjects With Exposure Beyond Cycle 4 in Study MMY 3021 Analysis Set)

Parameter	Vc (N=32) n (%)	Vc+Dex (N=121) n (%)
Any treatment-emergent adverse event	29 (91)	106 (88)
Any Grade ≥3 treatment-emergent adverse event	10 (31)	44 (36)
Any serious treatment-emergent adverse event	2 (6)	19 (16)
Any medication-related treatment-emergent adverse event	25 (78)	89 (74)
Treatment termination due to treatment-emergent adverse event[a]	4 (13)	19 (16)

Vc=VELCADE; Dex=dexamethasone;

[a] The cycle reported is the one in which the particular adverse event had action taken on VELCADE or dexamethasone as 'permanent stop'.

A subject is counted as having an event within a particular cycle if a new onset of the event occurred within the cycle.

Note: Percentages calculated with the number of subjects in each group as denominator.

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The incidence of treatment-emergent adverse events leading to treatment discontinuation were similar (≤10% difference) between the Vc+Dex and the VELCADE monotherapy groups (16% versus 13%, respectively), despite the large difference in the number of subjects between the 2 groups (121 versus 32).

The most common adverse events that resulted in treatment discontinuation in the Velcade-Dexamethasone group were peripheral sensory neuropathy and thrombocytopenia; each occurred in 6% of subjects.

2.5.1. Discussion on clinical safety

As expected, the toxicity profile of the combination Velcade-Caelyx was worse than that of bortezomib monotherapy. Twenty per cent of subjects discontinued study treatment in the bortezomib arm due to adverse events compared to 27% of subjects in the Caelyx-bortezomib arm.

However, toxicities observed within the Caelyx-bortezomib combination group were predictable, manageable, and consistent with the known safety profiles of both agents. No unexpected safety concerns were observed.

Dose reductions of bortezomib were required for 35% of subjects in the monotherapy group, compared with 39% of subjects in the combined group.

The safety profile of the Velcade-Caelyx combination at the time of the clinical cut-off of study MMY-3001 is confirmed by the post-marketing data collected since 2007.

With regard to the combination of Velcade and dexamethasone, the same limitations highlighted during the discussion of clinical efficacy partly apply to the discussion of clinical safety. These limitations relate to the non-comparative design of the MMY-2045 study and different characteristics of patient populations. Direct assessment of the possibly increased toxicity of Vc+ Dex compared to Vc alone is therefore not possible based on this study.

As expected, peripheral oedema, hyperglycemia and diabetes mellitus, common side effects of dexamethasone, were more frequent in the Velcade-Dexamethasone group of Study MMY-2045 than in the Velcade monotherapy group of Study MMY-3001.

No excess deaths were recorded between combination therapy and Velcade monotherapy groups (23% versus 25%, respectively). The most common cause of death was progressive disease (13% versus 20%, respectively). However, in the Velcade-Dexamethasone group there was a higher incidence of deaths due to adverse events. This was possibly attributable to the fact that patients in the Velcade-dexamethasone group were older, had a worse ECOG score, a higher tumour burden and a worse prognosis.

Overall, the safety results described from the Vc + Dex combination seem to be in line compared to Vc alone.

2.5.2. Conclusions on clinical safety

Based on this review, the adverse drug reactions observed with the combination treatment regimens were consistent with the known safety profiles of each drug administered in monotherapy. Section 4.8 of the SmPC is updated to reflect the safety database considered in this application.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan:

The PRAC considered that the risk management system is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The MAH implemented the changes requested in the RMP by PRAC and/or CHMP. The CHMP endorsed the changes to the Risk Management Plan with the following:

Safety concerns

Important identified risks	Heart failure Hepatotoxicity Acute hypersensitivity reaction Tumour lysis syndrome Peripheral motor neuropathy (including paralysis) Autonomic neuropathy Acute diffuse infiltrative pulmonary disease Pericardial disease Pulmonary hypertension Herpes zoster infection Posterior reversible encephalopathy syndrome Optic neuropathy and different degrees of visual impairment (up to blindness)
Important potential risks	Progressive multifocal leukoencephalopathy Ventricular rhythm abnormalities Guillain-Barré syndrome Other central nervous system disorders Medication/dispensing errors
Important missing information	Safety in patients with cardiac impairment or with NYHA Class III or IV impairment Safety in patients with ECOG>2 Second primary malignancies with VcTD induction therapy

Pharmacovigilance plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
VEL-PMS-JPN-1 Special Drug Use Results Survey of VELCADE Injection 3 mg (this trial has a specific focus on pulmonary complications associated with VELCADE treatment)/ Phase 4 Study. [Category 3]	The safety and efficacy of this product was assessed under actual use in Japan. In particular, events with potential differences in the tendency of development of adverse drug reactions from those observed in overseas clinical trials and events which are considered to warrant special caution after administration was investigated as priority items.	Priority items of investigation: 1. Investigation of acute pulmonary disorders/interstitial pneumonia with respect to development, factors affecting development, and measures taken at the time of development. 2. Development of the following: cardiac function disorders, peripheral neuropathy, haemotoxicity, pyrexia, skin disorders, hypotension, development of gastrointestinal disorders, and development of tumour lysis syndrome.	Started: 01 December 2006 Last patient last visit: 31 March 2011	Study was completed. Final study report submission date Jan 2017
VEL2U/ Drug Use-results Survey for VELCADE Injection 3mg in untreated multiple myeloma (MM) patients/ Phase 4 Study. [Category 3]	The purpose of this survey is to research actual use of VELCADE and to investigate the safety of VELCADE under actual conditions of its use in untreated MM patients in Japan	Main observation Items: patient background, medical history, concomitant medication and therapy for primary disease, administration record of VELCADE, adverse events, patient status, transplantation, antitumour effect and outcome	In Progress Started: 01 Nov 2011	Final study report submission date Jan 2017.

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks:		
Heart failure	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	should be closely monitored. SmPC: Labelled in Section 4.8 Undesirable Effects.	
Hepatotoxicity	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that rare cases of hepatic failure have been reported in patients receiving multiple concomitant medicinal products 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. SmPC: Labelled in Section 4.8 Undesirable Effects.	None
Acute hypersensitivity reaction	The SmPC, Section 4.3 Contraindications includes hypersensitivity to bortezomib, boron, or to any of the excipients. The SmPC, Section 4.8 Undesirable Effects, identifies hypersensitivity, anaphylactic shock, Type III immune complex mediated reaction as uncommon or rare adverse reactions.	None
Tumour lysis syndrome	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells, the complications of TLS may occur. The SmPC indicates that patients at risk of TLS are those with high tumour burden prior to treatment and suggests that these patients should be monitored closely and appropriate precautions taken. SmPC: Labelled in Section 4.8 Undesirable Effects.	None
Peripheral motor neuropathy (including paralysis)	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that treatment with VELCADE is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. The SmPC provides a recommendation	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	that patients be carefully monitored for symptoms of neuropathy and those patients experiencing new or worsening peripheral neuropathy may require the dose and schedule of VELCADE to be modified. Recommendations for dose modification in patients with neuropathy are provided in the SmPC, Section 4.2, Posology and Method of Administration. SmPC: Labelled in Section 4.8 Undesirable Effects.	
Autonomic neuropathy	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that 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.	None
Acute diffuse infiltrative pulmonary disease	The use of VELCADE is contraindicated in patients with acute diffuse infiltrative pulmonary disease in Section 4.3 of the SmPC. The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that there have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology in patients receiving VELCADE and that some of these events have been fatal. The SmPC recommends that a pretreatment chest radiograph be performed to determine if any additional diagnostic measures are necessary and to serve as a baseline for potential post-treatment pulmonary changes. SmPC: Labelled in Section 4.8 Undesirable Effects.	None
Pericardial disease	As stated in Section 4.3 of the SmPC, the use of VELCADE is contraindicated in patients with pericardial disease. The SmPC, Section 4.8 Undesirable Effects, identifies pericarditis as adverse reactions based on reports from postmarketing sources.	None
Pulmonary hypertension	The SmPC, Section 4.8 Undesirable	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Effects, identifies pulmonary hypertension as a serious adverse reaction uncommonly reported during treatment with VELCADE.	
Herpes zoster infection	Section 4.4 of the SmPC indicates that antiviral prophylaxis should be considered in patients being treated with VELCADE. The SmPC, Section 4.8 Undesirable Effects, identifies herpes zoster (including disseminated) as a common adverse reaction during treatment with VELCADE.	None
Posterior reversible encephalopathy syndrome	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that there have been reports of PRES in patients receiving VELCADE. Section 4.4 of the SmPC describes PRES as a rare, often reversible, rapidly evolving neurological condition which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging, is used to confirm the diagnosis. The SmPC indicates that in patients developing PRES, VELCADE should be discontinued. The safety of reinitiating VELCADE treatment in patients previously experiencing PRES is not known. SmPC: Labelled in Section 4.8 Undesirable Effects.	None
Optic neuropathy and different degrees of visual impairment (up to blindness)	The proposed SmPC, Section 4.8 Undesirable Effects, identifies optic neuropathy, different degrees of visual impairment (up to blindness) as an adverse reaction based on reports from clinical trial and postmarketing sources.	None
Important potential risks:		
Progressive multifocal leukoencephalopathy	In Section 4.4 of the SmPC, managing physicians are advised to monitor patients regularly for any new or worsening neurological symptoms or signs that may be suggestive of PML, and refer appropriately.	None
Ventricular rhythm	The SmPC, Section 4.4 Special	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
abnormalities	Warnings and Precautions for Use warns that isolated cases of QT-prolongation have been reported during treatment with VELCADE. Arrhythmia and ventricular dysfunction are identified as uncommon adverse drug reactions on the basis of postmarketing reports in Section 4.8 (Undesirable Effects) of the SmPC.	
Guillain-Barré Syndrome	None	None
Other central nervous system disorders	The SmPC, Section 4.8 Undesirable Effects, identifies encephalopathy as an adverse reaction based on reports from postmarketing sources.	None
Medication/Dispensing errors	<u>Subcutaneous administration</u> The proposed SmPC, Section 6.6 Special Precautions for Disposal and Other Handling, provides instructions for HCPs on reconstitution of the 10 mL vial of VELCADE for either IV or SC injection. Additionally, warnings regarding the danger of intrathecal administration are included in Sections 4.2, 4.4 and 6.6 of the proposed SmPC. There is also single vial packaging with an additional warning statement, and single labelling for IV and SC administrations of VELCADE.	Additional risk-minimisation activities, including: Education of HCPs Reconstitution poster, A dosing slide rule Training of medical representative, medical and scientific liaisons.
	<u>Confusion with administering the incorrect regimens in the transplant induction setting</u> Refer to the proposed SmPC (Sections 4.2 and 4.8) for the correct use of the 2 regimens (VELCADE with dexamethasone and with dexamethasone and thalidomide) and for additional information concerning ADRs.	Proposed actions/components and rationale include: The company will ensure proper training of all MSLs on the different VELCADE treatment schedules approved for transplant induction. MSLs will be able to offer on-site training and relevant recommendations. Have the schedules, doses and number of cycles for each of the 2 combinations clearly described and graphically represented in educational materials. Include detailed discussions on the dosing regimens in the transplant induction setting in all future regional and local medical education (programme) whenever the use of VELCADE in the

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		Transplant settings is addressed.
Important missing information:		
Safety in patients with cardiac impairment or with NYHA Class III or IV impairment	The SmPC, Section 4.4 Special Warnings and Precautions for Use, states that acute development or exacerbation of congestive heart failure, and/or new onset of decreased LVEF has been reported during bortezomib treatment. In a single agent Phase 3 randomised, comparative trial the incidence of heart failure in the VELCADE (injected intravenously) 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.	None
Safety in patients with ECOG>2	None	None
Second primary malignancies with VcTD induction therapy	Section 4.4 of the SmPC warns that when VELCADE is given in combination with other medicinal products. The prescriber should refer to the SmPC for these other products.	None

2.7. Update of the Product information

As a consequence of these new indications, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The CHMP agreed with the following indication. Section 4.1 of the SmPC has been amended accordingly:

*VELCADE as monotherapy **or in combination with pegylated liposomal doxorubicin or dexamethasone** is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.*

In addition, Annex II has been modified to add the key elements with regards to the induction transplant regimens to minimise the risk of medication errors.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to other tested versions of the Velcade Package Leaflet. The bridging report submitted by the applicant has been found acceptable.

In addition, the list of local representatives in the PL has been updated.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The beneficial effect of the combination of Velcade and with pegylated liposomal-doxorubicin 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 haematopoietic stem cell transplantation is supported by data from Study MMY-3001. A protocol defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45 % (95 % CI; 29 57 %, p < 0.0001) for patients treated with combination therapy of VELCADE and pegylated liposomal doxorubicin. The median TTP was 6.5 months for the VELCADE monotherapy patients compared with 9.3 months for the VELCADE plus pegylated liposomal doxorubicin combination therapy patients. These results, though not mature, constituted the protocol defined final analysis.

Results from the Phase 2 study MMY-2045 showed a higher ORR (mainly VGPR) at cycle 4 in 70% of patients receiving the Velcade-dexamethasone group (n=144) compared to those patients who were randomised at cycle 5 to Velcade-dexamethasone plus other agents.

The positive trend in favour of Velcade-dexamethasone group (n=121) was confirmed by the supportive study MMY-3021 showing a higher ORR recorded from cycle 5 onward compared to dexamethsone monotherapy by cycle 4 (n=101). However in this latter study, the addition of dexamethasone was allowed only after 4 cycles.

The trend of an higher efficacy of the combination regimen vs Velcade monotherapy was further confirmed by matched pair analyses comparing the Velcade-dexamethasone treatment (study MMY-2045), and the Velcade single agent therapy (studies APEX and MMY-3001). The matched pair analyss with 127 pairs showed improved ORR (CR+PR) (odds ratio 3.769; 95% CI 2.045-6.947; p < 0.001), PFS (hazard ratio 0.511; 95% CI 0.309 0.845; p=0.008), TTP (hazard ratio 0.385; 95% CI 0.212 0.698; p=0.001) for VELCADE in combination with dexamethasone over VELCADE monotherapy.

Uncertainty in the knowledge about the beneficial effects

No formal evaluations of the clinical pharmacology and dose finding of Velcade in combination with Caelyx or dexamethasone have been performed.

No direct comparison has been submitted between Velcade and Velcade-dexamethasone in the claimed indication. In addition, pitfalls in the design of study MMY-3021 do not allow to exclude that improvement of ORR in Velcade-dexamethasone group is due to the increased number of Velcade cycles since dexamethasone was allowed only from cycle 5 onwards. However, supportive evidence was provided in a matched pair analysis based on appropriate covariate selection.

Risks

Unfavourable effects

As expected the toxicity profile of the two combinations was higher than when bortezomib was given alone.

Toxicities observed within the Caelyx-bortezomib combination group were predictable, manageable, and consistent with the known safety profiles of both agents. At the time of the clinical data collection

cut-off date on April 2006, 12% subjects had died in the Bortezomib monotherapy arm compared with 9% of deaths in the Caelyx-bortezomib combination arm.

The addition of dexamethasone did not exacerbate the adverse effects of Velcade, but exerted its own characteristic side effects. In particular, it was shown to precipitate hyperglycemia/diabetes mellitus and facilitate the development of infections, particularly pneumonia that was the most common treatment-emergent serious adverse event reported in 5% of subjects in the Velcade-Dexamethasone group in study MMY-3021. The overall frequency of Grade 3 and 4 treatment-emergent adverse events in Study MMY-2045 was high, but not higher than the Velcade monotherapy arm of Study MMY-3001.

In the Velcade-dexamethasone group there was a higher incidence of deaths (33.7% vs 25.2%); this was confirmed by the matched pair analysis on 127 pairs (33.9% vs 31.5%). The incidence of treatment-emergent adverse events leading to death (Grade 5) was higher for the combination of Velcade-dexamethasone compared to Velcade monotherapy. This was possibly attributable to the fact that patients in the Velcade-dexamethasone group were older, had a worse ECOG score, a higher tumour burden and a worse prognosis.

Uncertainty in the knowledge about the unfavourable effects

No uncertainties about the side effect profile of the combinations Velcade-Caelyx and Velcade-dexamethasone emerged from the submitted studies.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

As regard the combination Velcade-Caelyx the strength of the evidence in favour of efficacy is considered sufficient to support the proposed extension ofindication. Similarly the safety profile is considered well characterized and overall manageable thus allowing a positive evaluation of this combination therapy.

Regarding the combination Velcade-dexamethasone, it cannot be excluded that a bias in the recruitment of patients due to the non randomised nature of study MMY-2045 might have resulted in the selection of a patient population more prone to benefit from the combination therapy (e.g. less pre-treated patients, with more sensitive disease, eligible to stem cell transplantation). This could have incorrectly amplified the magnitude of the effect of the combination treatment. However, supportive evidence was provided in a matched pair analysis based on appropriate covariate selection.

No exacerbation of the adverse effects of Velcade was observed with the addition of dexamethasone which exerted its own characteristic side effects which summed up to those of Velcade. The combination with dexamethasone was associated with a risk of developing fatal complications, particularly pneumonia. However, the heterogeneous nature of causes of death do not point to a specific toxicity of the combination treatment. Most of the deaths were registered more than 30 days after the last dose of Velcade, thus the combination therapy does not seem to increase the risk of death during the treatment or shortly after.

Benefit-risk balance

In both combination treatments, Velcade-Caelyx and Velcade-dexamethasone the efficacy is considered demonstrated and the safety profile sufficiently characterised and manageable.

Discussion on the Benefit-Risk Balance

The overall B/R of Velcade in combination with pegylated liposomal-doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation is positive.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extensions of indication for Velcade in combination with pegylated liposomal doxorubicin or in combination with dexamethasone in patients with relapsed and /or progressive multiple myeloma who have received at least 1 prior therapy. Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The package leaflet has been updated accordingly. Editorial changes were also made to the product information. Annex II has also been corrected to add the key elements with regards to the induction transplant regimens to minimise the risk of medication errors. The list of local representatives in the package leaflet has also been updated.

The requested group of variations proposed amendments to the SmPC, Annex II and Package Leaflet.

This CHMP recommendation is subject to the following amended conditions:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• Additional risk minimisation measures

In each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the national competent authority.

The MAH shall ensure thatall healthcare professionals involved in the prescribing, dispensing, handling or administration of VELCADE are provided with educational material.

The educational material shall consist of the following:

- SmPC
- Reconstitution, dosing and administration booklet
- Reconstitution poster
- Dosing Slide Rule
- Induction Transplant Regimens Graph.

The Reconstitution, dosing and administration booklet shall contain the following key elements:

- VELCADE 3.5 mg can be administered both intravenously and subcutaneously while VELCADE 1 mg can be administered only intravenously
- different reconstitution requirements for intravenous (IV) or subcutaneous (SC) use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted VELCADE (both IV and SC use) required for different body surface areas (cross reference to Dosing Slide Rule)
- advice on method of administration for both IV and SC use, including the need to rotate injection sites for SC use
- storage precautions for reconstituted solution
- potential risks of administration errors including overdosing, underdosing and that inadvertent intrathecal administration has resulted in death
- to report any adverse event, or medication error experienced with the administration of VELCADE 3.5 mg.

The Reconstitution poster shall contain the following key elements:

- different reconstitution requirements for VELCADE 3.5 mg IV or SC use
- need to handling the medicinal product in sterile setting
- storage precautions for reconstituted solution
- advice on how to reduce the risk of mix-up of IV and SC reconstituted syringes

- that VELCADE is to be given only by IV or SC injections; no other route of administration is allowed
- that VELCADE 1 mg is only for IV use
- to report any adverse event, or medication error experienced with the administration of VELCADE 3.5 mg.

Dosing Slide Rule shall contain the following key elements:

- a dose-calculation tool that enables prescribers to input a patient's height and weight in order to calculate the body surface area (BSA) and thereby to determine the appropriate VELCADE dose
- different reconstitution requirements for intravenous (IV) or subcutaneous (SC) use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted VELCADE (both IV and SC use) required for different body surface areas.

Induction Transplant Regimens Graph shall contain the following key elements:

- instructions for prescribing and administration including the cycles' length and number of cycles, to minimise the risk of medication and dispensing errors potentially induced by the existence of the two different bortezomib combination regimens in the Transplant Induction Setting (VELCADE plus dexamethasone, and VELCADE plus dexamethasone and thalidomide).
- to remind that patients receiving VELCADE in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide, with reference to the SmPC of thalidomide for additional information.

• Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.