London, 27 June 2013
EMA/416707/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VELCADE

International non-proprietary name: BORTEZOMIB

Procedure No. EMEA/H/C/000539/II/0059

Note

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

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Correction made by EPL: Grade >3 adverse events was changed to Grade ≥3 adverse events

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List of abbreviations

allo-SCT	allogenic stem cell transplant(ation)
auto-SCT	autologous stem cell transplant(ation)
CAD	cyclophosphamide, doxorubicin (Adriamycin), and dexamethasone
CR	complete response
DCEP	dexamethasone, cyclophosphamide, etoposide or etoposide phosphate, and cis-platinum
ECOG	Eastern Cooperative Oncology Group
ERA	Environmental risk assessment
EU	European Union
G-CSF	granulocyte-colony stimulating factor
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto
GMMG	German Multiple Myeloma Group
HDM	high-dose melphalan
HDT	high-dose chemotherapy
HOVON	Dutch-Belgian Stichting Hemato-Oncologie voor Volwassenen Nederland; Cooperative Trial Group for Hematology Oncology
HR	hazard ratio
IFM	Intergroupe Francophone du Myélome
Ig	immunoglobulin
ISS	International Staging System
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	odds ratio
OS	Overall survival
PETHEMA	Programa para el Estudio de la Terapéutica en Hemopatía Maligna
PFS	progression free survival
PO	per os/by mouth
PR	partial response
SOC	system organ class
TD	thalidomide, dexamethasone
VAD	vincristine, doxorubicin (Adriamycin), and dexamethasone
VBAD	vincristine, bis-chloronitrosourea, doxorubicin (Adriamycin), and dexamethasone
VBMCP	vincristine, bis-chloronitrosourea, melphalan, cyclophosphamide, and prednisone
Vc	Velcade
VcAD	Velcade, doxorubicin (Adriamycin), and dexamethasone
VcD	Velcade and dexamethasone
VcDC	Velcade, dexamethasone, cyclophosphamide
Vc-MP	Velcade, melphalan, and prednisone
VcTD	Velcade, thalidomide, and dexamethasone
VGPR	very good partial response

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 11 April 2012 an application for a variation 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 variation was requested:

Variation 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

Extension of indication for Velcade in combination with chemotherapy medicinal products for the induction treatment of adult patients with previously untreated multiple myeloma prior to high-dose chemotherapy and stem cell transplantation.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/345/2010 on the granting of a class waiver.

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 and the evaluation teams were:

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

Submission date:	11 April 2012
Start of procedure:	22 April 2012
Rapporteur's preliminary assessment report circulated on:	16 June 2012
Co-Rapporteur's preliminary assessment report circulated on:	15 June 2012
The CHMP adopted a report on similarity of Velcade with Thalidomide Celgene and Revlimid	21 June 2012
Joint Rapporteur's updated assessment report circulated on:	13 July 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 July 2012
MAH's responses submitted to the CHMP on:	10 October 2012
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	9 December 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	13 December 2012
MAH's responses submitted to the CHMP on:	27 February 2013
Joint Rapporteur's assessment report on the MAH's responses circulated on:	5 April 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 April 2013
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2013
MAH's responses submitted to the CHMP on:	22 May 2013
Joint Rapporteur's assessment report on the MAH's responses circulated on:	18 June 2013
CHMP opinion:	27 June 2013

2. Scientific discussion

2.1. Introduction

Multiple Myeloma (MM) is a progressive rare haematologic 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.

The median survival time is approximately 4 to 5 years (2 years after relapse). Current treatment options aim not only to improve survival but also to inhibit tumour progression and delay disease-related complications.

Morbidity and mortality were strongly reduced by the application of autologous stem cell transplantation (ASCT) which provided improvement to melphalan and prednisone (MP) treatments of choice for several decades. Since SCT can induce complete remissions and prolong survival, most treatment guidelines currently recommend incorporating high-dose chemotherapy (HDT)/SCT into initial therapy programs for patients < 65 years old, and to consider HDT/SCT for patients 65 to 70 years with good performance status and manageable comorbidities.

The choice of induction therapy prior to HDT/ASCT varies and consolidation and maintenance therapies are given following ASCT. The objective of induction treatment is to rapidly de-bulk the tumour without causing damage to the haematopoietic progenitor cells in order to achieve the best possible response before transplantation. A good induction response is correlated with improved progression-free survival (PFS) and overall survival (OS) outcomes; regimens that maximize clinical response and increase PFS and OS are needed.

Historically, induction therapies have been based upon combinations of corticosteroids, vincristine, alkylating agents (such as melphalan or cyclophosphamide) and carmustine. Specific induction therapy regimens commonly used in the past included single-agent high-dose dexamethasone, adriamycin-dexamethasone, vincristine-adriamycin-dexamethasone (VAD), pegylated liposomal doxorubicin-vincristine-dexamethasone, and cyclophosphamide-idarubicin-dexamethasone. The overall response rate associated with VAD induction is in the range of 55% to 60%. However, the post-induction complete response (CR) rate with traditional induction regimens such as VAD is 5% to 10%. No chemotherapeutic agents are currently approved in Europe specifically for induction treatment of MM.

Velcade (bortezomib) is a reversible proteasome inhibitor used in the treatment of Multiple Myeloma (MM). It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades poly-ubiquitinated proteins. The catalytic core of the 26S proteasome is the 20S proteasome. The ubiquitin-proteasome pathway plays an essential role in orchestrating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death. The mechanisms by which Velcade elicits its antitumour activity may vary among tumour types, according to the extent to which each affected pathway is critical to the inhibition of tumour growth. Specifically, Velcade is thought to be efficacious in MM via its inhibition of nuclear factor κB activation, its attenuation of interleukin-6-mediated cell growth, a direct apoptotic effect, and possibly through antiangiogenic and other effects.

Velcade is currently authorised in the EU for the following indications:

> Velcade 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 bone marrow transplantation.
>
> Velcade in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.

In this application, the MAH of Velcade proposed to extend the indication of Velcade *in combination with chemotherapy medicinal products for the induction treatment of adult patients with previously untreated multiple myeloma prior to high-dose chemotherapy and stem cell transplantation*.

This was supported by 3 pivotal studies and one supportive study of Velcade in combination with either dexamethasone, adriamycin and dexamethasone or thalidomide and dexamethasone.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

The Applicant provided an environmental risk assessment (ERA) in agreement with Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) to support this type II variation. According to this Guideline, drug substances with a log Pow > 4.5 should be screened for persistence (P), bioaccumulation (B) and toxicity (T) according to the European Chemicals Bureau.

Phase I: the partition coefficient octanol/water, log Pow, of bortezomib is 2 (pH=7), which is lower than the trigger value of 4.5. Consequently, no PBT-assessment is performed.

The worst case surface water Predicted Environmental Concentration (PECsurfacewater) for bortezomib, assuming no degradation or removal in sewage sludge treatment, is 0.32 µg/L. After refinement with market penetration data, for which the Applicant calculated that, approximately 19'500 -20'000 patients will receive bortezomib as treatment for their disease and estimated that the consumption for all bortezomib treated patients in EU in the peak year 2016 will be approximately 1.92 kg/year and 5252 mg/day, the PECsurfacewater was calculated to be 0.0052 x 10-3 µg/L.

As the PECsurfacewater of bortezomib is in orders of magnitude below the threshold value of 0.01 µg/L, no further testing in the aquatic environment (phase II) is required.

2.2.2. Discussion on non-clinical aspects

Based on the ERA presented, the addition of a new indication for Velcade as induction treatment prior to stem cell transplantation for patients with newly diagnosed multiple myeloma is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of bortezomib. Considering the above data, bortezomib is not expected to pose a risk to the environment.

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 – Summary of design of studies

	Integrated Data			Published Data
	Hovon/GMMG MMY-3003 (Cooperative Study Group Protocol number HOVON65MM/GMMG-HD4)	**IFM 2005-01**	**Pethema MMY-3010** (Cooperative Study Group Protocol number GEM05MENOS65)	**GIMEMA MMY-3006** (Cooperative Study Group Protocol number MM-BO2005)[8]
	Mod5.3.5.1\MMY-3003	Mod5.3.5.1\IFM 2005-01	Mod5.3.5.1\MMY-3010	
Design	randomized, open label, multicenter, Phase 3 1:1 single randomization for induction & maintenance, stratified by study center and ISS stage	randomized, open label, multicenter, Phase 3 1:1:1:1 single randomization stratified by initial β2 microglobulin and presence of chromosome 13 abnormalities	randomized, open label, multicenter, Phase 3 1:1:1 randomization for induction 1:1:1 re-randomization for maintenance	randomized, open label, multicenter, Phase 3 1:1 single randomization for induction and consolidation, stratified by ISS stage
Study Participants	men and women 18 to 65 years of age (inclusive) Previously untreated MM Durie-Salmon stage II or III WHO PS 0 to 3	men and women ≤65 years of age Previously untreated, newly diagnosed MM (SWOG criteria) Durie Salmon stage II or III, or stage I with symptomatic bone lesion measurable monoclonal spike in serum or urine ECOG PS 0 to 2	men and women ≤65 years of age Previously untreated, secretory MM (presence of monoclonal component in serum or urine, presence of clonal plasma cells in bone marrow or plasmacytomas, tissue or organ involvement related to MM) ECOG PS 0 to 2	men and women 18 to 65 years of age Previously untreated, symptomatic and measurable MM Karnofsky of at least 60%
Efficacy Endpoints	Responses were evaluated according to standard criteria.[5,12,36]			
Key (Primary)	– PFS (censored at allo-SCT)	– Post-induction CR+nCR rate	– Post-induction and post-SCT response rate (CR+nCR+PR) – Post-induction and post-SCT CR+nCR rate	– Post-induction CR+nCR rate
Other	– Post-induction and post-SCT response rate (CR+nCR+VGPR+PR) – OS – TTP	– Post-induction and post-SCT response rate (CR+nCR+VGPR+PR) – Post- SCT CR+nCR rate – OS – TTP – PFS	– PFS – OS – TTP	– Post-(second) SCT CR+nCR rate – Post-consolidation CR+nCR – TTP – PFS – OS

	Integrated Data			Published Data
	Hovon/GMMG MMY-3003 (Cooperative Study Group Protocol number HOVON65MM/GMMG-HD4)	**IFM 2005-01**	**Pethema MMY-3010** (Cooperative Study Group Protocol number GEM05MENOS65)	**GIMEMA MMY-3006** (Cooperative Study Group Protocol number MM-BO2005)[8]
Treatment Sequence	VAD induction/SCT/T maintenance VcAD induction/SCT/Vc maintenance (see Section 2.1, Figure 1)	VAD or VcD induction/SCT VAD or VcD induction/DCEP intensification/SCT (see Section 2.2, Figure 2)	VcTD or TD or VBMCP/VBAD/Vc induction/SCT re-randomization interferon α-2b or T or VcT maintenance (see Section 2.3, Figure 3)	VcTD or TD induction/double SCT/VcTD or TD consolidation (See Section 2.4)
Induction /Induction Intensification Regimens (and number of subjects randomized per treatment treatment group)	Treatment group A (n=416): VAD (3 cycles) **V** 0.4 mg (d1-4) **A** 9 mg/m^2 (d1-4) **D** 40 mg (d1-4, 9-12, 17-20) Treatment group B (n=417): VcAD (3 cycles) **Vc** 1.3 mg/m^2 (d1,4,8,11) **A** 9 mg/m^2 (d1-4) **D** 40 mg (d1-4, 9-12, 17-20)	Treatment group A1 (n=121): VAD (4 cycles) **V** 0.4 mg (d1-4) **A** 9 mg/m^2 (d1-4) **D** 40 mg (c1-2: d1-4, 9-12, 17-20); (c3-4: d1-4) Treatment group A2 (n=121): VAD+DCEP (4 cycles + 2 cycles) **VAD** same as A1 + **D** 40 mg (d1-4) **C** 400 mg/m^2 (d1-4) **E** 40 mg/m^2 (d1-4) **P** 15 mg/m^2 (d1-4) Treatment group B1 (n=121): VcD (4 cycles) **Vc** 1.3 mg/m^2 (d1,4,8,11) **D** 40 mg (c1-2: d1-4, 9-12); (c3-4: d1-4) Treatment group B2 (n=119): VcD+DCEP (4 cycles + 2 cycles) **VcD** - same as B1 **DCEP** - same asA2	Treatment group A (n=129): VBMCP-VBAD/Vc (alternating 4 cycles/2 cycles) not included in integrated analysis Treatment group B (n=127): TD (6 cycles) **T** 50 mg (d1-4); if tolerated, increased to 100 mg (d15-28), then 200 mg **D** 40 mg (d1-4, 9-12) Treatment group C (n=130): VcTD (6 cycles) **Vc** 1.3 mg/m^2 (d1,4,8,11) **T** 50 mg (d1-4); if tolerated, increased to 100 mg (d15-28), then 200 mg **D** 40 mg (d1-4, 8-11)	TD treatment group (n=239) (3 cycles) **T** 100 mg (d1-14); then 200 mg daily thereafter **D** 40 mg (d1-4, 9-12) VcTD treatment group (n=241) (3 cycles) **Vc** 1.3 mg/m^2 (d1,4,8,11) **T** 100 mg (d1-14); then 200 mg daily thereafter **D** 40 mg (d1,2,4,5,8,9,11,12)

	Integrated Data			Published Data
	Hovon/GMMG MMY-3003 (Cooperative Study Group Protocol number HOVON65MM/GMMG-HD4)	**IFM 2005-01**	**Pethema MMY-3010** (Cooperative Study Group Protocol number GEM05MENOS65)	**GIMEMA MMY-3006** (Cooperative Study Group Protocol number MM-BO2005)[8]
Post-SCT Regimens (and number of subjects who entered each phase)	**Maintenance** Treatment group A (n=271) **thalidomide** 50 mg/day or Treatment group B (n=229) **Vc** 1.3 mg/m^2 q2w for up to 2 years	No post-SCT (maintenance or consolidation) treatment administered as part of the study.	**Maintenance** (subjects were re-randomized) Treatment group M1 (n=92) **interferon α-2b** 1.5 MU 3 times/week or Treatment group M2 (n=89) **thalidomide** 100 mg/day or Treatment group M3 (n=90) **Vc** 1.3 mg/m^2 (d1,4,8,11 of every 3-month cycle and **thalidomide** 100 mg/day for up to 3 years	**Consolidation** (2 cycles) TD treatment group (n=180) **T** 100 mg daily **D** 40 mg (d1-4, 20-23) VcTD treatment group (n=187) **Vc** 1.3 mg/m^2 (d1,8,15,22) **T** 100 mg daily **D** 40 mg (d1,2,8,9,15,16,22,23) **Maintenance** **D** 40 mg (d1-4 q28days) (until relapse or progression)

A=Adriamycin (doxorubicin); B=BCNU (bis-chloroethylnitrosourea); c=cycle; C=cyclophosphamide; CR=complete response; d=day; D=dexamethasone; EBMT=European Treatment group for Blood and Marrow Transplantation; ECOG=Eastern Cooperative Oncology Treatment group; ISS=International Staging System; M=melphalan; MM=multiple myeloma; nCR=near CR; OS=overall survival; P=prednisone; PFS=progression-free survival; PR=partial response; PS=performance status; q2w=once every 2 weeks; q28days=every 28 days; SCT=stem cell transplantation; SWOG=Southwest Oncology Treatment group; T=thalidomide; TTP=time to progression; V=vincristine; Vc=VELCADE; VGPR=very good PR; vs=versus; WHO=World Health Organization
Note: the VcAD regimen in Study MMY-3003 was abbreviated as PAD in the protocol.

The total integrated efficacy population included 1,572 subjects, 787 of whom received Velcade-based induction treatment and 785 of whom received non-Velcade-based induction treatment. Published results from Study MMY-3006 included data from an additional 474 subjects, 236 of whom received Velcade-based induction treatment and 238 of whom received non-Velcade-based induction treatment.

2.4. Clinical efficacy

2.4.1. Dose response study

No new dose-finding study to support the proposed posology for Velcade in this new indication as induction for SCT eligible patients was performed.

The starting dose of Velcade 1,3 mg/m^2 was chosen according to the currently approved Velcade dose for treatment of patients with previously untreated multiple myeloma in combination with other agents (that also applies to the monotherapy regimen in patients who have received at least 1 prior therapy).

The numbers and duration of cycles were different in the studies submitted.

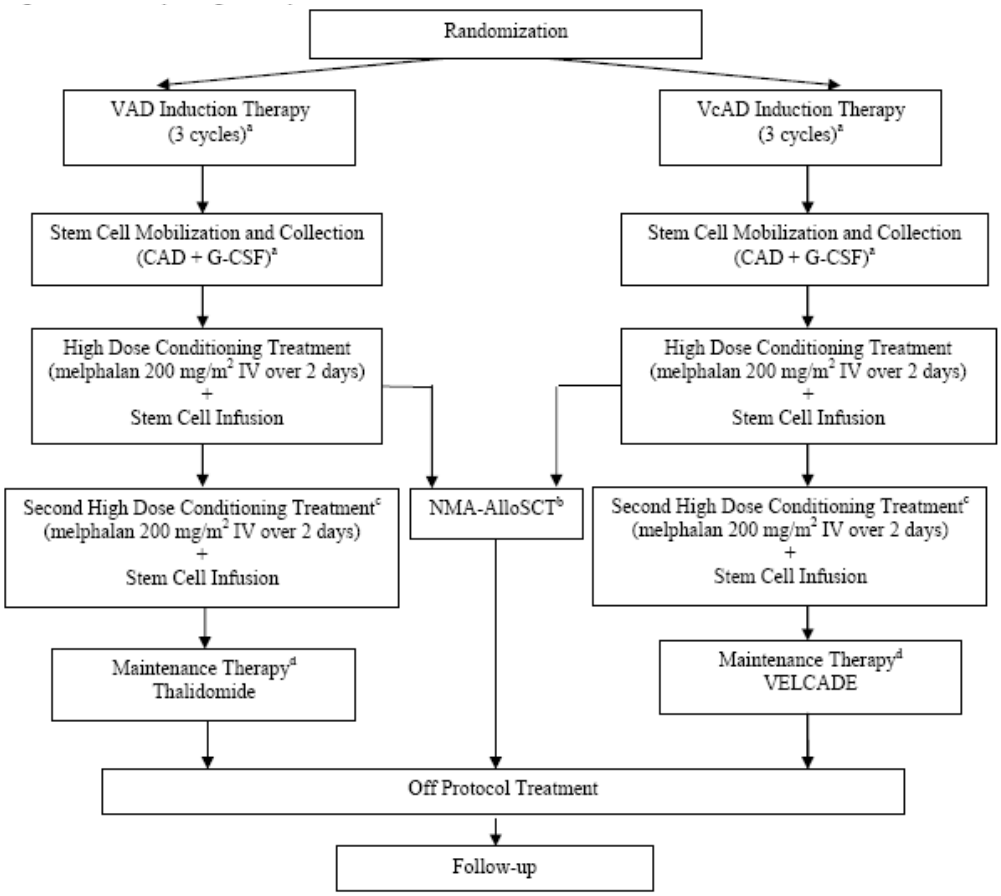
2.4.2. Main studies

Study MMY-3003 (HOVON/GMMG)

Methods

Study MMY-3003 was an open-label randomised phase 3 study on the effect of bortezomib combined with Adriamycin (doxorubicin), Dexamethasone for Induction Treatment, Followed by High-Dose Melphalan, and Bortezomib Alone During Maintenance in Patients With Multiple Myeloma.

Figure 1 – Study MMY-3003 design



CAD=cyclophosphamide (1,000 mg/m^2 IV on Day 1), doxorubicin (Adriamycin) (15 mg/m^2 IV on Days 1-4), dexamethasone (40 mg on Days 1-4); G-CSF=granulocyte-colony stimulating factor (10 µg/kg on Day 5 to last pheresis); HDM=high-dose melphalan; HLA=human leukemia antigen haplotype; IV=intravenous(ly); NMA-AlloSCT=non-myeloablative allogenic stem cell transplantation; Q2W=once every 2 weeks; VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcAD=VELCADE, Adriamycin, dexamethasone

[a] Subjects who did not meet the inclusion criteria for CAD or HDM but with a complete response (CR), partial response (PR), minimal response (MR), or no change (NC) might proceed with 3 more cycles of VAD (Treatment A) or VcAD (Treatment B), followed by thalidomide maintenance (Treatment A) or VELCADE maintenance (Treatment B) for 2 years until progression.

[b] Subjects with a HLA-identical family donor who met the eligibility criteria proceeded with NMA-AlloSCT after the first course of HDM and SCT.

[c] For subjects who achieve at least a PR. This was applicable to HOVON centers only. GMMG centers performed a second HDM procedure for all subjects regardless of response after first HDM.

[d] Maintenance therapy was given for up to 2 years.

Source: Mod5.3.5.1\MMY-3003\Fig1

Study participants

Subjects enrolled in this study were required to meet the following acceptance criteria: Patients with a confirmed diagnosis of multiple myeloma stage II or III according to the Salmon & Durie criteria; Age 18 to 65 years, inclusive; WHO performance status 0 to 3 (WHO=3 was allowed only when caused by multiple myeloma and not by comorbid conditions).

Subjects with the following were excluded from the study: known intolerance of thalidomide or boron, systemic amyloid light-chain amyloidosis, non-secretory multiple myeloma, and previous chemotherapy or radiotherapy except 2 cycles of melphalan/prednisone or local radiotherapy in case of local myeloma progression.

Treatments

This study consisted of 3 phases for each study subject: induction treatment phase, high-dose chemotherapy with auto SCT phase and maintenance treatment phase.

Enrolled subjects received up to 3 cycles (28 days/cycle) of induction treatment as vincristine, Adriamycin and dexamethasone (VAD) or Velcade, Adriamycin and dexamethasone (VcAD). Approximately 4 to 6 weeks after the start of the third induction treatment cycle, eligible subjects were to undergo stem cell mobilization and collection with a regimen of CAD, and granulocyte-colony stimulating factor (G-CSF). High-dose melphalan (HDM) was to occur between 6 and 8 weeks after stem cell collection.

Subjects who underwent double transplantation received a second course of HDM between 2 and 3 months after the first course when the subject achieved at least a partial response (PR).

Maintenance treatment was to begin 4 weeks after the last course of HDM and continue for up to 2 years or until disease progression occurred. Maintenance treatment was also to be terminated for subjects who did not achieve at least minimal response (MR) at 6 months after starting maintenance treatment. After completion of study treatment, subject data were followed-up for the collection of survival status and disease progression information.

Objectives

The objectives were to assess the efficacy of Velcade combined with intensive chemotherapy and in maintenance therapy in comparison with intensive therapy with vincristine followed by thalidomide maintenance in subjects with previously untreated multiple myeloma, as measured by the progression-free survival (PFS); To evaluate the overall response rate and CR + very good partial response (VGPR) both after induction treatment and after autologous transplant (auto-SCT); To evaluate overall survival (OS) and to assess the safety and toxicity of Velcade combined with intensive chemotherapy and in maintenance therapy.

Outcomes/endpoints

The primary efficacy endpoint was PFS with censoring at the time of allo-SCT (PFSC): 1-year, 2-year, and 3-year.

Subjects with progression before HDM but who obtained at least a PR on HDM were not counted as an event. Subjects who received allo-SCT before progression/relapse were censored at the date of transplantation. Subjects known to be still alive and free of progression at the last day of contact were censored at that time.

The secondary endpoints were response rate (CR/nCR) post-induction (i.e after induction before HDM) and post-transplant (i.e. after HDM/auto-SCT). Response rate after second transplant was also a secondary endpoint for subjects who had undergone a second transplant.

The secondary endpoint OS was defined as the interval between the date of randomisation and the date of death from any cause.

PFS without censoring at allo-SCT and PFS from the time of HDM were also considered at 1-year, 2-year, and 3-year, as well as time to progression.

Investigator assessment of response was done according to EBMT, IBMTR, and ABMTR criteria (Bladé et al. 1998) after the third VcAD or VAD course, after stem cell collection, and after each course of

HDM. During maintenance treatment, disease status was evaluated every 2 months. According to the response criteria, response was required to be confirmed after 6 weeks. However, this requirement was not applied to the response measurements after the third VcAD or VAD course, after stem cell collection, and between the 2 courses of HDM, as the treatment intervals were too short.

Complete response (CR) required all of the following:

- Absence of the original monoclonal paraprotein (M-Protein) in serum and (10 x concentrated) urine by immunofixation, maintained for at least 6 weeks
- Less than 5% plasma cells in a representative bone marrow aspirate or otherwise in a bone marrow biopsy. Only in subjects with non-secretory myeloma, bone marrow investigations were to be repeated after an interval of 6 weeks to confirm CR
- No increase in size or number of lytic bone lesions (development of compression fractures did not exclude CR)
- Disappearance of any soft tissue plasmacytoma

nCR was not defined in the protocol but derived afterwards. A response of VGPR/PR (as captured on the CRF) was re-coded as nCR if it fulfilled all criteria for CR except a negative immunofixation (either positive or unknown/not done).

Very good partial response (VGPR) required meeting the criteria for PR but show a 90% reduction of serum M-Protein concentration for at least 6 weeks.

Partial response (PR) required all of the following:

- 50% reduction of serum M-Protein concentration maintained for at least 6 weeks
- Reduction in 24 hours urine M-Protein either by >=90% or to <200 mg, maintained for at least 6 weeks
- In subjects with non-secretory myeloma, >=50% reduction in plasma cells in a representative bone marrow aspirate, or otherwise bone marrow biopsy, maintained for at least 6 weeks
- 50% reduction in size of soft tissue plasmacytoma
- No increase in size or number of lytic bone lesions (development of compression fractures did not exclude PR)

Sample size

The sample size calculation was based on the assumption that the PFS at 3 years for subjects in the control group was 50%, and PFS in the experimental group was 60%, which corresponds to a relative hazard rate of 0.74. The number of events needed to detect a hazard rate of 0.74 with a power of 80% and significance level 0.049 (2-sided and adjusted for 1 interim analysis at a significance level of 0.001) was 356. Assuming that 10% of subjects would receive allogenic transplantation, this number of events was expected to be reached with the inclusion of 800 subjects in 3 years and an additional follow up of 2 years. A significance level of 0.05 was used for other efficacy endpoints. All tests were 2-sided.

Randomisation

Randomisations were balanced with a biased-coin minimization procedure ensuring balance within each stratum and overall balance. Initially, the minimization was based on study centre, Salmon & Durie Stage (2 versus 3), and LDH level (≤ULN versus >ULN of LDH). After the third protocol amendment, the minimization was based on study centre and ISS stage (I versus II versus III).

Blinding (masking)

Not applicable.

Statistical methods

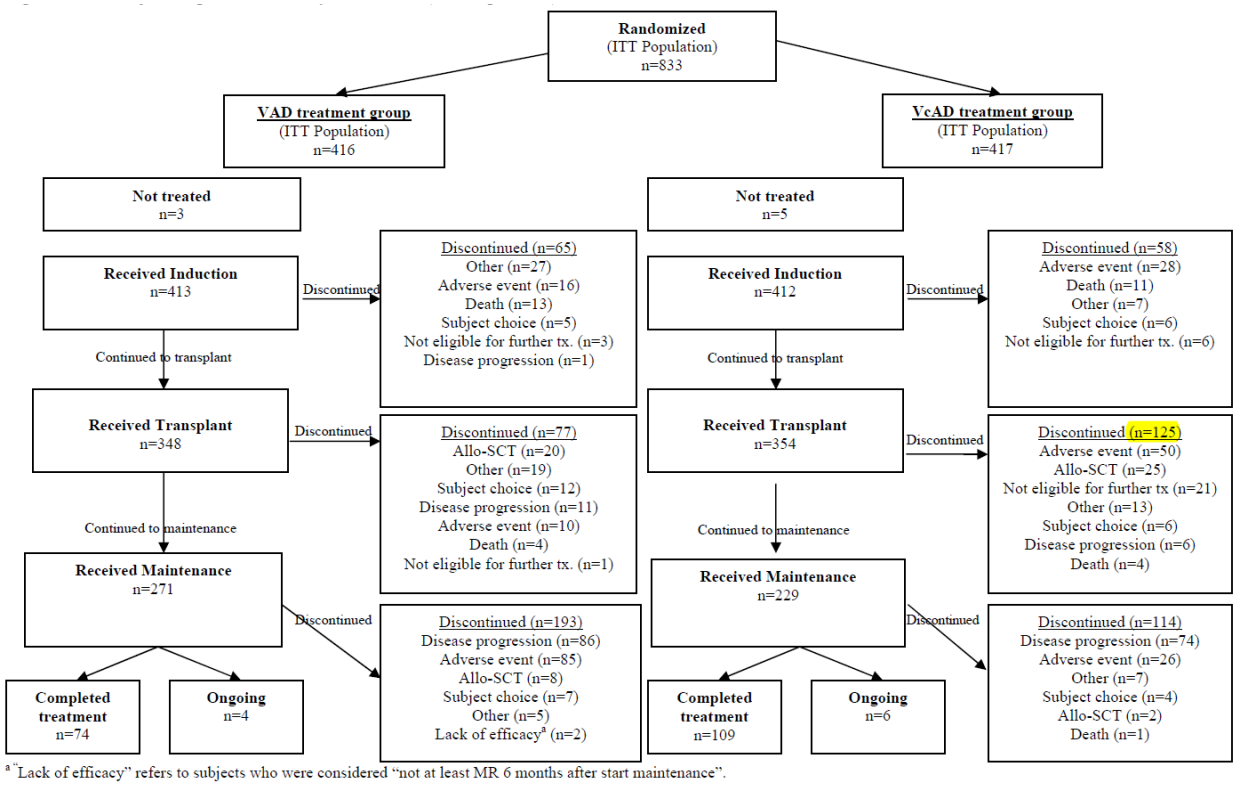
Three analysis populations were used in this study: the intent-to-treat (ITT) analysis set, evaluable analysis set, and safety analysis set. The ITT analysis set, which included all randomised subjects, was used for demographic summaries and efficacy analyses. The safety analysis set for the Induction Phase included all randomised subjects who received at least one dose of induction study treatment. The safety analysis set for the Transplant Phase included all randomised subjects who received at least 1 HDM/auto-SCT. The safety analysis set for the Maintenance Phase included all randomised subjects who received at least one dose of maintenance drug.

The primary treatment comparison was based on a stratified log-rank test. Stratification factor was to include ISS (I versus II versus III versus unknown), which was derived using data reported in the case report form (CRF). The hazard ratio (HR) and its 95% confidence interval (CI) were determined to estimate the treatment effect using the stratified Cox regression analysis. For each treatment group, 1-year, 2-year, and 3-year PFS rate were estimated using Kaplan-Meier method, and a 95% CI was computed. Analyses similar to those described for the primary efficacy endpoint were used for all secondary endpoints, except response rate, where comparisons of the response rate between the 2 treatment groups were made using the stratified Cochran-Mantel-Haenszel (CMH) test. Response rate and its associated 95% CI were to be provided for each treatment group. Safety of the treatment groups was compared using the incidence and severity of adverse events, and laboratory test results. Adverse event severity was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0.

Results

Participant flow

Figure 2 – Subject disposition in Study MMY-3003 (ITT population)



[a] "Lack of efficacy" refers to subjects who were considered "not at least MR 6 months after start maintenance".

For both the VAD and VcAD treatment groups, the median duration of induction treatment was 11 weeks: in both arms, 99% subjects were included in the Induction Phase safety analysis set.

The median duration of maintenance treatment was 14 months in the VAD treatment group and 22 months in the VcAD treatment group. Maintenance treatment was discontinued after 6 months in subjects who did not achieve at least a Minimal Response. The median duration of follow-up was 42 months for both the VAD and VcAD treatment group.

Recruitment

Study period: 4 May 2005 - 12 April 2011

Conduct of the study

There were 5 protocol amendments. One key recommendation by the Data and Safety Monitoring Board (DSMB) was to mandate prophylactic anti-viral therapy for the VcAD treatment group and was implemented with Protocol Amendment 4.

Baseline data

Demographic and baseline characteristics are presented in the table below.

Table 2 – Demographic and baseline characteristics (Study 26866138-MMY-3003: Intent-to-Treat Analysis Set)

	---- VAD ---- (N=416)	--- VcAD --- (N=417)	--- Total --- (N=833)
Age (years)			
N	416	417	833
Category, n (%)			
<55	161 (39)	151 (36)	312 (37)
≥55	255 (61)	266 (64)	521 (63)
Mean (SD)	55.1 (7.62)	55.5 (7.06)	55.3 (7.34)
Median	57.0	57.0	57.0
Range	(25;65)	(31;65)	(25;65)
Sex, n (%)			
N	416	417	833
Male	248 (60)	257 (62)	505 (61)
Female	168 (40)	160 (38)	328 (39)
Weight (kg)			
N	413	413	826
Mean (SD)	79.3 (14.68)	78.1 (15.33)	78.7 (15.01)
Median	79.0	76.0	77.8
Range	(45;138)	(42;170)	(42;170)
Height (cm)			
N	413	413	826
Mean (SD)	173.4 (9.74)	173.5 (9.53)	173.4 (9.63)
Median	174.0	174.0	174.0
Range	(142;200)	(145;202)	(142;202)
Body surface area (m^2)			
N	414	413	827
Mean (SD)	1.93 (0.206)	1.92 (0.206)	1.92 (0.206)
Median	1.90	1.90	1.90
Range	(1.4;2.6)	(1.3;2.5)	(1.3;2.6)
WHO performance score, n (%)			
N	413	412	825
0	183 (44)	195 (47)	378 (46)
1	175 (42)	171 (42)	346 (42)
2	47 (11)	31 (8)	78 (9)
3	8 (2)	15 (4)	23 (3)

VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcAD=VELCADE, doxorubicin (Adriamycin), dexamethasone; WHO=World Health Organization

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Thirty-eight percent of subjects in both the VAD and VcAD treatment groups entered the study with ISS Stage I disease; 34% and 40%, respectively, entered with Stage II disease; and 28% and 22%, respectively, entered with Stage III disease. The median baseline urine monoclonal paraprotein (M-protein) level was higher among subjects in the VAD treatment group (460 mg/24hours) compared with the VcAD treatment group (240 mg/24 hours). For both the VAD and VcAD treatment groups, the median duration of treatment for the Induction Phase was 11 weeks, and the median number of cycles received was 3 cycles.

Numbers analysed

Table 3 – Number of subjects per analysis set

(Study 26866138-MMY-3003: All Randomized Subjects Analysis Set)

	VAD (N=416) n (%)	VcAD (N=417) n (%)	Total (N=833) n (%)
Intent-to-Treat analysis set	416 (100)	417 (100)	833 (100)
Treated	413 (99)	412 (99)	825 (99)
Evaluable analysis set	408 (98)	409 (98)	817 (98)
Safety analysis set for induction	411 (99)	410 (98)	821 (99)
Safety analysis set for transplant	347 (83)	352 (84)	699 (84)
Received auto-SCT	315 (76)	322 (77)	637 (76)
Received allo-SCT	32 (8)	30 (7)	62 (7)
Safety analysis set for maintenance	270 (65)	229 (55)	499 (60)

VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcAD=VELCADE, doxorubicin (Adriamycin), dexamethasone; auto-SCT=autologous stem cell transplant; allo-SCT=allogeneic stem cell transplant

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

Six subjects were randomized but appeared not eligible afterwards for reasons of non-secreting myeloma, misdiagnosis or prior treatment.

Four out of these 6 subjects were treated but excluded from safety analysis sets due to unavailability of safety data.

Outcomes and estimation

Results of the primary end point PFSC and secondary endpoints are presented in the table below.

Table 4 – Summary of key efficacy results (Study MMY-3003)

ITT Analysis Set	VAD (N=416)	VcAD (N=417)	OR (95% CI); p-value[c]
Post-induction response rate			
CR	2.9 (1.5, 5.0)	11.0 (8.2, 14.4)	4.21 (2.20, 8.04); <0.001
CR+nCR	6.3 (4.1, 9.0)	18.2 (14.6, 22.3)	3.40 (2.12, 5.45); <0.001
Overall response (CR+nCR+VGPR+PR)	61.3 (56.4, 66.0)	84.2 (80.3, 87.5)	3.32 (2.38, 4.62); <0.001
Post-transplant response rate			
CR	12.3 (9.3, 15.8)	22.5 (18.6, 26.9)	2.11 (1.45, 3.08); <0.001
CR+nCR	19.7 (16.0, 23.9)	32.6 (28.1, 37.3)	2.00 (1.45, 2.76); <0.001
Overall response (CR+nCR+VGPR+PR)	65.9 (61.1, 70.4)	77.5 (73.1, 81.4)	1.74 (1.28, 2.36); <0.001
Progression-free survival (mos) - censored[a,b]			HR (95% CI); p-value[d]
Median (95% CI)	28.1 (24.8, 31.8)	35.0 (30.8, 39.2)	0.76 (0.63, 0.91); 0.003
1-year PFS rate	80.1 (75.9, 83.7)	88.1 (84.5; 90.9)	---
2-year PFS rate	56.1 (51.0, 61.0)	66.8 (61.8, 71.3)	
3-year PFS rate	40.1 (35.0, 45.2)	48.2 (42.9, 53.3)	---
Overall survival (mos)[a]			
Median (95% CI)	NE (59.9, NE)	NE (63.9, NE)	0.82 (0.63, 1.05); 0.120
1-year OS rate	89.3 (85.9, 91.9)	92.4 (89.4, 94.6)	
2-year OS rate	81.4 (77.3, 84.8)	85.7 (81.9, 88.8)	
3-year OS rate	71.6 (66.8, 75.9)	78.4 (73.9, 82.2)	---
Time to progression (TTP) (mos)[a]			
Median (95% CI)	31.7 (27.4, 35.4)	37.4 (33.3, 39.8)	0.79 (0.65, 0.95); 0.010

CR=complete response; nCR=near complete response; PFS=progression-free survival; HR=hazard ratio; ITT=intent to treat; mos=months; NE=not estimable; OR=odds ratio; OS=overall survival; PR=partial response; VAD=vincristine, Adriamycin (doxorubicin), dexamethasone; VcAD=VELCADE, Adriamycin (doxorubicin), dexamethasone; VGPR=very good partial response

[a] Based on Kaplan-Meier product limit estimates; includes Maintenance Phase treatment: thalidomide in the VAD treatment group and Vc in the VcAD treatment group.

[b] Censored at the time of allogeneic stem cell transplant.

[c] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel chi-squared test.

[d] HR for PFS, OS, and TTP based on a Cox's model stratified by International Staging System (ISS) class; p-value by Log-rank test stratified by ISS class.

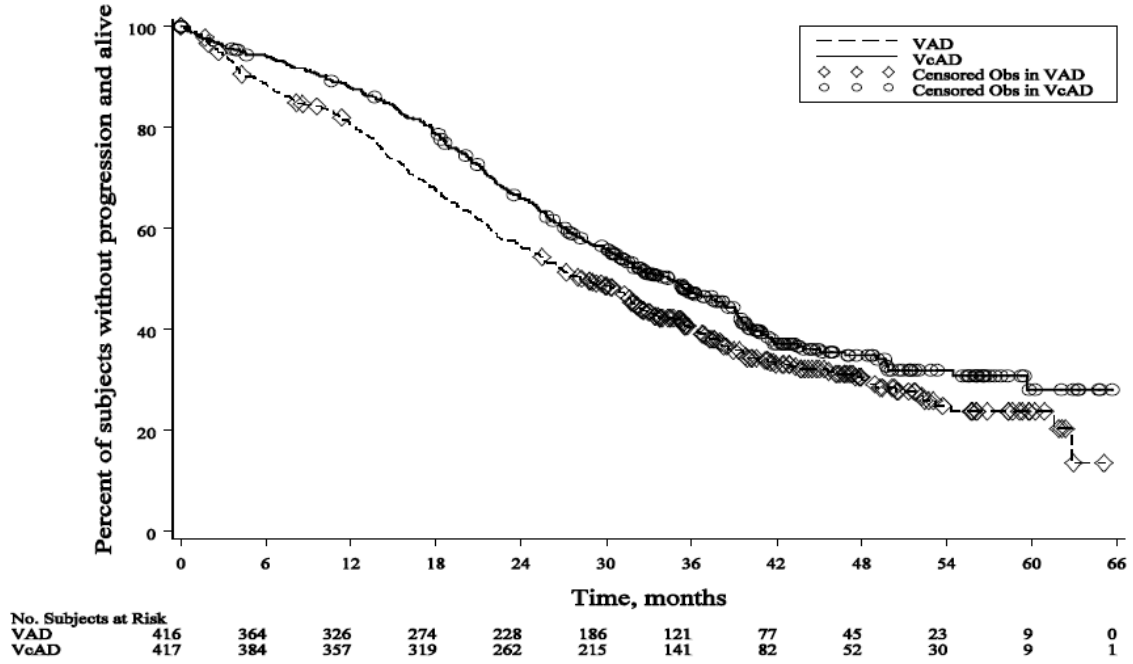
Note: A HR <1or OR>1 indicates an advantage for VcAD.

PFS without censoring at allo-SCT

The median PFS was longer in the VcAD treatment group compared with the VAD treatment group; 29 months (95% CI: 25.2, 31.8) in the VAD treatment group and 35 months (95% CI: 30.7, 38.3) in the VcAD treatment group (HR=0.80; 95% CI: 0.67, 0.95; p=0.012).

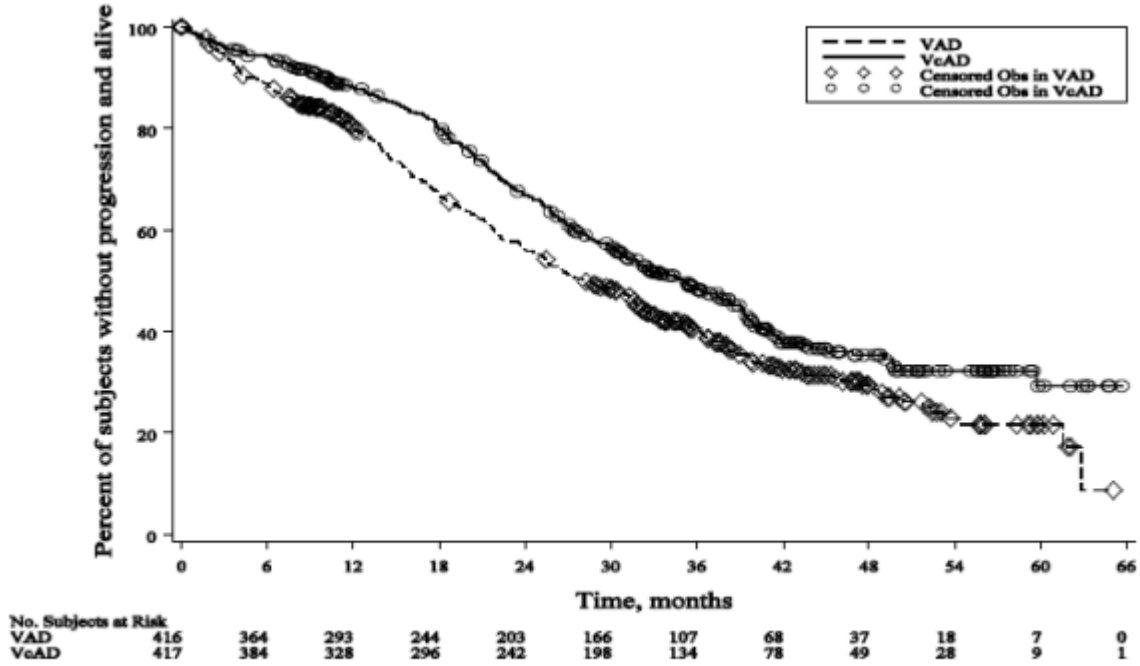
Higher % of censored was observed in VcAD treatment group (41.7% vs 34.4% in the VAD treatment group).

Figure 3 – Kaplan-Meier Plot of Progression-Free Survival Without Censoring at Allo-SCT (Study MMY-3003 ITT analysis set)



VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcAD=VELCADE, doxorubicin (Adriamycin), dexamethasone; allo-SCT=allogeneic stem cell transplant

Figure 4 – Kaplan-Meier Plot of Progression-Free Survival With Censoring at Allo-SCT (Study MMY-3003 ITT analysis set)



VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcAD=VELCADE, doxorubicin (Adriamycin), dexamethasone; allo-SCT=allogeneice stem cell transplant
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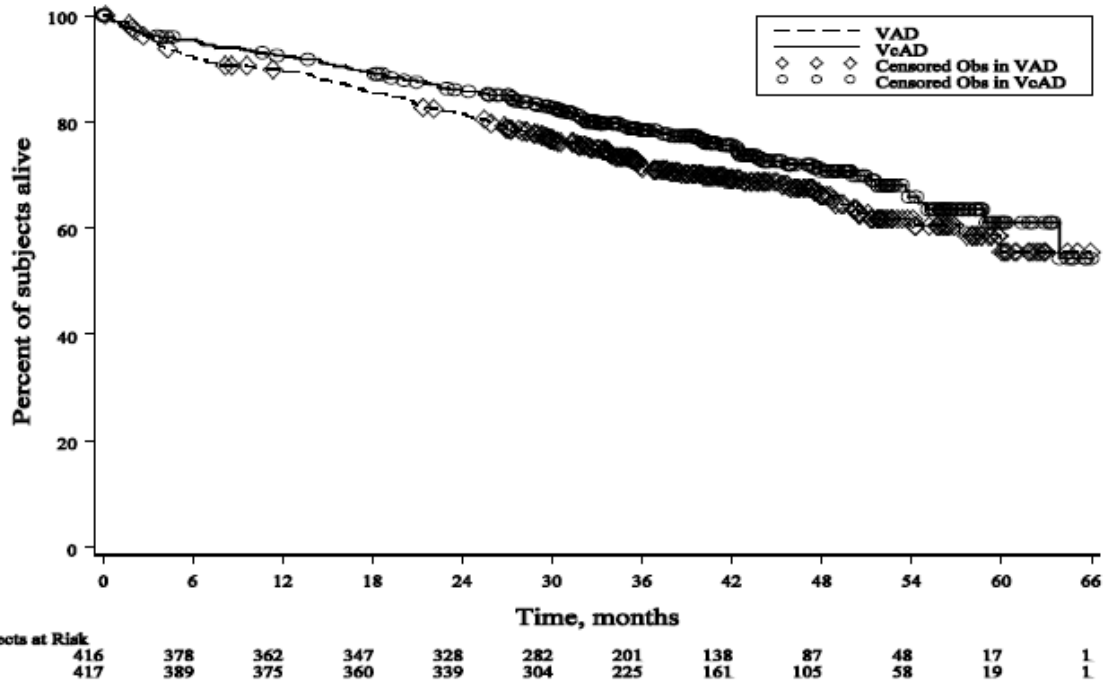
PFS from the time of HDM

By the 12 April 2011 clinical cutoff date, the median PFS was longer in the VcAD treatment group compared with the VAD treatment group; 26 months (95% CI: 22.1, 31.7) in the VAD treatment group and 31 months (95% CI: 26.7, 33.9) in the VcAD treatment group (HR=0.82; 95% CI: 0.67, 1.00; p=0.052).

Higher % of censored was observed in VcAD treatment group (45% vs 38% in the VAD treatment group).

Overall survival

Figure 5 – Kaplan-Meier Plot of Overall Survival (Study MMY-3003 ITT analysis set)



VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcAD=VELCADE, doxorubicin (Adriamycin), dexamethasone
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Ancillary analyses

PFSC and PFS, relative to baseline stratification factors, demographic data (sex and age) and disease characteristics (ISS staging and cytogenetic abnormalities), were evaluated as planned.

The HR for each subgroup analysed was consistently <1, suggesting that the risk for a PFSC or PFS event was lower in the VcAD treatment group than in the VAD treatment group in all the subgroups examined, in particular, among the subgroups with ISS Stage III, high-risk cytogenetics, renal insufficiency (creatinine clearance <60 mL/min), and in male. Therefore, the magnitude of the subgroup-specific treatment effects was consistent with the overall analyses of PFSC and PFS.

When considering the cytogenetic classification VAD treatment seems to be more effective (PFS) on high risk patients and with renal insufficiency (creatinine clearance <60 mL/min).

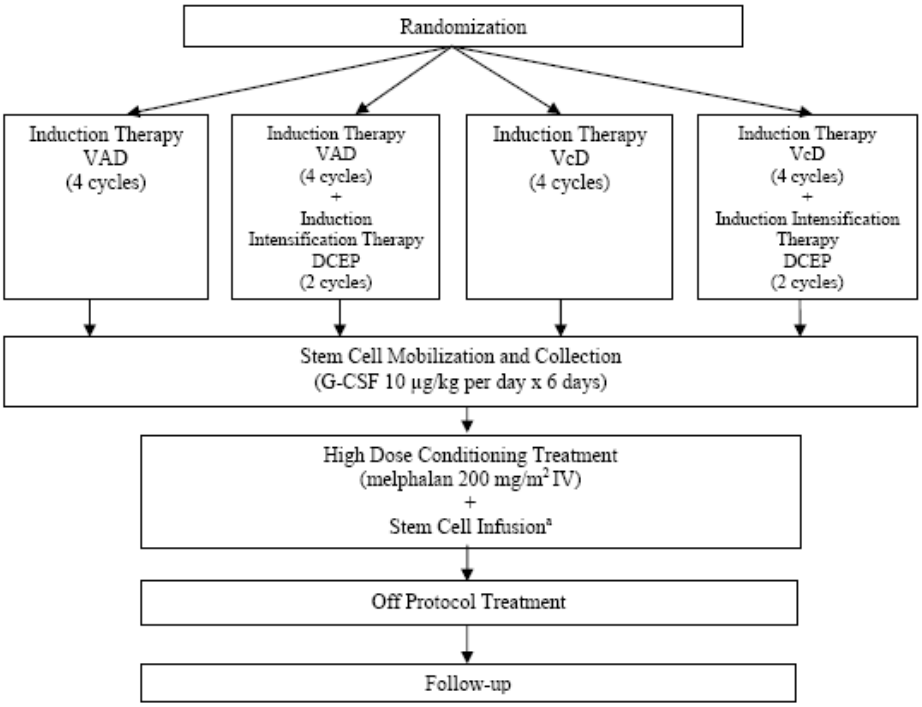
The results from all other secondary efficacy endpoints and subgroup analyses were also consistently in favor of VcAD treatment. There was a trend towards a benefit in OS, but median OS was not reached in either of the treatment groups.

Study IFM 2005-01 (IFM)

Methods

Study IFM 2005-01 was an Open-label, multicentre, randomised phase 3 study to compare the combination of Velcade and dexamethasone (VcD) with VAD in the treatment of patients up to the age of 65 with newly diagnosed multiple myeloma.

Figure 6 – Study IFM 2005-01 design



AlloSCT=allogenic stem cell transplantation; DCEP= dexamethasone, cyclophosphamide, etoposide or etoposide phosphate, and cis-platinum; G-CSF=granulocyte-colony stimulating factor; HDM=high-dose melphalan; HLA= human leukemia antigen haplotype; IV=intravenous(ly); SCT=stem cell transplant; VAD=vincristine, Adriamycin, and dexamethasone; VcD=VELCADE (1.3 mg/m^2) and dexamethasone

[a] Subjects could receive up to 2 SCTs. Subjects with a less than very good partial response (VGPR) 1 to 3 months after the first SCT were eligible to receive a second SCT. Subjects with less than a partial response (PR) received a second SCT. Subjects with a PR received a second stem cell transplant; unless the subject had a donor with a matching HLA haplotype, in which case, AlloSCT was performed.

Note: for the scope of the meta analysis, arms were merged in order to form 2 homogeneous arms in terms of regimens.

Study participants

Subjects enrolled in this study were required to have newly diagnosed multiple myeloma according to Southwest Oncology Group (SWOG) criteria, have not been previously treated apart from local

radiotherapy in case of a threatening or incapacitating lesion and/or a 4-day block of dexamethasone in case of emergency, and have a measurable monoclonal spike (>10 g/L in the serum or 0.2 g/24 hour in the urine).

Subjects with the following were excluded from the study: Stage 1 indolent myeloma, ECOG performance status >2, history of cancer, confirmed amyloidosis positive HIV serology, peripheral neuropathy NCI Grade ≥2, and use of an investigational medicinal product during 30 days prior to inclusion.

Treatments

Enrolled subjects were randomised to receive either VAD or VcD for up to 4 cycles of induction treatment (28-day cycles for VAD or 21-day cycles for VcD) with or without an additional 2 cycles of induction intensification treatment, followed by stem cell mobilization, collection, and transplant. Eligible subjects underwent 1 to 2 SCTs preceded by HDT with melphalan as conditioning treatment. No maintenance treatment was included in this study.

Objectives

The primary objective was to compare the complete response/near complete response (CR/nCR) rate (with negative or positive immunofixation) obtained with the VAD or VcD combination used as induction treatment in subjects up to the age of 65 years with newly diagnosed multiple myeloma.

Outcomes/endpoints

The primary efficacy endpoint of the study was post-induction CR+nCR rate. The response criteria were adapted from the EBMT criteria (Bladé et al., 1998).

Secondary efficacy endpoints included post-induction and post-transplant CR/nCR, VGPR, or PR), PFS and OS.

Sample size

Approximately 480 subjects were to be enrolled to ensure 440 subjects were to be included in the analysis. With 440 subjects and a 2- sided $\alpha=0.05$ (significance level of the statistical test), the study would have a power of 80% to detect a difference of 10% in the rate of CR/nCR between induction treatment with four cycles (assuming a CR/nCR rate of 20% versus 10%, respectively).

Randomisation

The subjects were randomly assigned to 1 of the following 4 treatment groups: VAD with no induction intensification; VAD followed by induction intensification with dexamethasone, cyclophosphamide, etoposide or etoposide phosphate and cis-platinum (DCEP); VcD with no induction intensification and VcD followed by induction intensification with DCEP.

Randomisation was performed centrally and was stratified on the basis of the initial β2 microglobulin level (> or ≤3 mg/L) and the presence of chromosome 13 abnormalities identified by FISH analysis.

Blinding (masking)

Not applicable.

Statistical methods

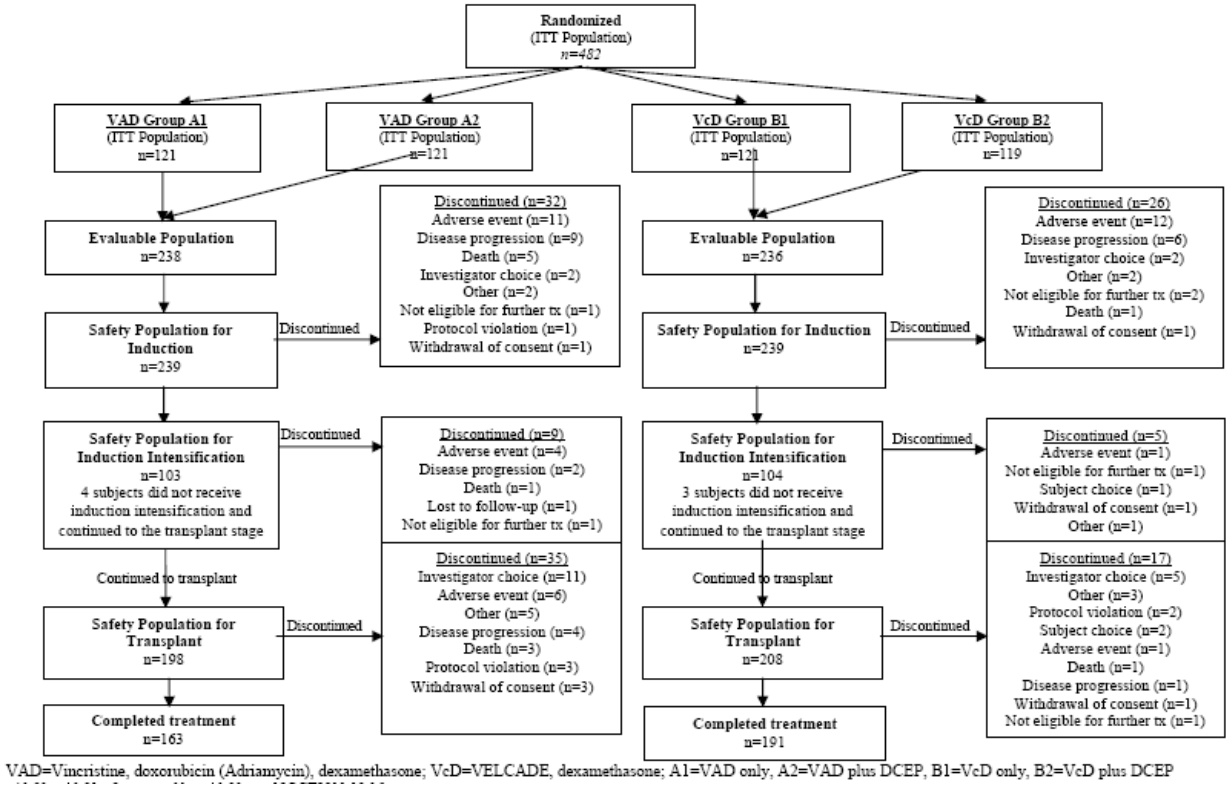
For the primary efficacy endpoint, a significance level of 0.0475 was used, taking into account 1 interim analysis. A significance level of 0.05 was used for other efficacy endpoints. The primary treatment comparison (post-induction CR/nCR rate) was based on a stratified Cochran-Mantel-Haenszel (CMH) test. Response rate and its associated 95% confidence interval (CI) were to be provided for each treatment group. Analyses similar to those described for the primary endpoint were used for all secondary endpoints. For each treatment group, 1-year, 2-year, and 3-year PFS rates were estimated using the Kaplan-Meier method, and a 95% CI was computed. The primary treatment comparison was based on a stratified log-rank test. The hazard ratio (HR) and its 95% CI were determined to estimate the treatment effect using the stratified Cox regression analysis.

Three analysis populations were defined as intent-to-treat (ITT) analysis set, evaluable analysis set, and safety analysis set. The ITT analysis set, which included all randomised subjects, was used for demographic summaries and efficacy analyses.

Results

Participant flow

Figure 7 – Subject disposition in Study IFM 2005-01 (ITT population)



VAD=Vincristine, doxorubicin (Adriamycin), dexamethasone; VcD=VELCADE, dexamethasone; A1=VAD only, A2=VAD plus DCEP, B1=VcD only, B2=VcD plus DCEP

Recruitment

Study period: 04 July 2005 - 05 June 2009

Conduct of the study

There were 5 protocol amendments.

Baseline data

Demographic characteristics were similar between the treatment groups. The median age was 57 years in both groups (range: 26 to 65 years), with 60% of subjects ≥55 years of age. The study population was 55% men and 45% women. At baseline, median body surface area was similar in both treatment groups (1.80 m^2 in the VAD group and 1.90 m^2 in the VcD group), and the majority (88%) had a World Health Organization (WHO) performance status score of ≤1.

Baseline disease characteristics were similar between the treatment groups. Across the VAD and VcD groups, the subtypes of myeloma at baseline included IgG (62% and 60%, respectively), IgA (22% in both groups), and light chain (13% and 15%, respectively). The rest of the subtypes of multiple myeloma were reported in ≤2% of subjects. Across the VAD and VcD groups, subjects entered the study with similar ISS Stage disease: Stage I (42% and 43%, respectively); Stage II (35% and 33%, respectively), and Stage III (23% and 25%, respectively). The median baseline serum M-protein level was 3.64 g/dL and 3.41 g/dL for the VAD and VcD groups, respectively).

The median duration of treatment was 13 weeks for the VAD group and 11 weeks for the VcD group. The median number of cycles received for both groups was 4 cycles.

Numbers analysed

Table 5 – Number of subjects per analysis set

(Study IFM 2005-01:All Randomized Subjects Analysis Set)

	VAD			VcD			
	A1 (N=121) n (%)	A2 (N=121) n (%)	A1+A2 (N=242) n (%)	B1 (N=121) n (%)	B2 (N=119) n (%)	B1+B2 (N=240) n (%)	Total (N=482) n (%)
Intent-to-Treat	121 (100)	121 (100)	242 (100)	121 (100)	119 (100)	240 (100)	482 (100)
Evaluable	120 (99)	118 (98)	238 (98)	118 (98)	118 (99)	236 (98)	474 (98)
Safety for induction	121 (100)	118 (98)	239 (99)	120 (99)	119 (100)	239 (>99)	478 (99)
Safety for induction intensification	0	103 (85)	103 (43)	0	104 (87)	104 (43)	207 (43)
Safety for transplant	100 (83)	98 (81)	198 (82)	106 (88)	102 (86)	208 (87)	406 (84)

VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcD=VELCADE, dexamethasone; A1=VAD only, A2=VAD plus DCEP, B1=VcD only, B2=VcD plus DCEP

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

Transplants were all auto-SCT.

A dose reduction of Velcade occurred in 13% of subjects in the VcD group (6% for adverse events, 3% for "other" reasons. Dose reductions of vincristine did not occur in the VAD group.

Outcomes and estimation

Results are presented in the table below.

Table 6 – Summary of key efficacy results (Study IFM 2005-01)

ITT Analysis Set	VAD (N=242) % (95% CI)	VcD (N=240) n (%) (95% CI)	OR (95% CI); p-value[a]
Post-induction response rate			
CR	1.2 (0.3, 3.6)	5.4 (2.9, 9.1)	4.71 (1.31, 16.93); 0.010
CR+nCR	6.2 (3.5, 10.0)	14.6 (10.4, 19.7)	2.58 (1.37, 4.85); 0.003
Overall response (CR+nCR+VGPR+PR)	60.7 (54.3, 66.9)	77.1 (71.2, 82.2)	2.18 (1.46, 3.24); <0.001
Post-transplant response rate			
CR	10.3 (6.8, 14.9)	18.3 (13.6, 23.8)	1.95 (1.15, 3.29); 0.011
CR+nCR	23.1 (18.0, 29.0)	37.5 (31.4, 44.0)	1.98 (1.33, 2.95); 0.001
Overall response (CR+nCR+VGPR+PR)	74.4 (68.4, 79.8)	79.6 (73.9, 84.5)	1.34 (0.87, 2.05); 0.179
	Median (95% CI)	Median (95% CI)	HR (95% CI); p-value[b]
Progression-free survival (mos)[c]			
Median (95% CI)	29.7 (26.3, 37.2)	36.1 (32.5, 41.1)	0.78 (0.60, 1.01); 0.058
1-year PFS rate	81.7 (76.3, 86.1)	89.6 (85.0, 92.8)	---
2-year PFS rate	61.8 (55.3, 67.6)	69.9 (63.6, 75.3)	
3-year PFS rate	43.5 (36.3, 50.5)	50.0 (42.0, 57.5)	---
Overall survival (mos)[c]			
Median (95% CI)	NE	NE	0.88 (0.58, 1.35); 0.561
1-year OS rate	91.7 (87.4, 94.6)	95.4 (91.9, 97.4)	---
2-year OS rate	86.7 (81.7, 90.4)	90.4 (85.9, 93.5)	
3-year OS rate	77.3 (70.0, 83.1)	81.4 (74.8, 86.3)	NE
Time to progression (mos)[c]			
Median (95% CI)	30.6 (27.2, 38.5)	37.3 (33.6, 41.2)	0.78 (0.60, 1.02); 0.069

CR=complete response; HR=hazard ratio; ITT=intent to treat; mos=months; nCR=near complete response; NE=not estimable; OR=odds ratio; OS=overall survival; PFS=progression-free survival; PR=partial response; TTP=time to progression; VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcD=VELCADE, dexamethasone; VGPR=very good partial response

[a] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel chi-squared test.

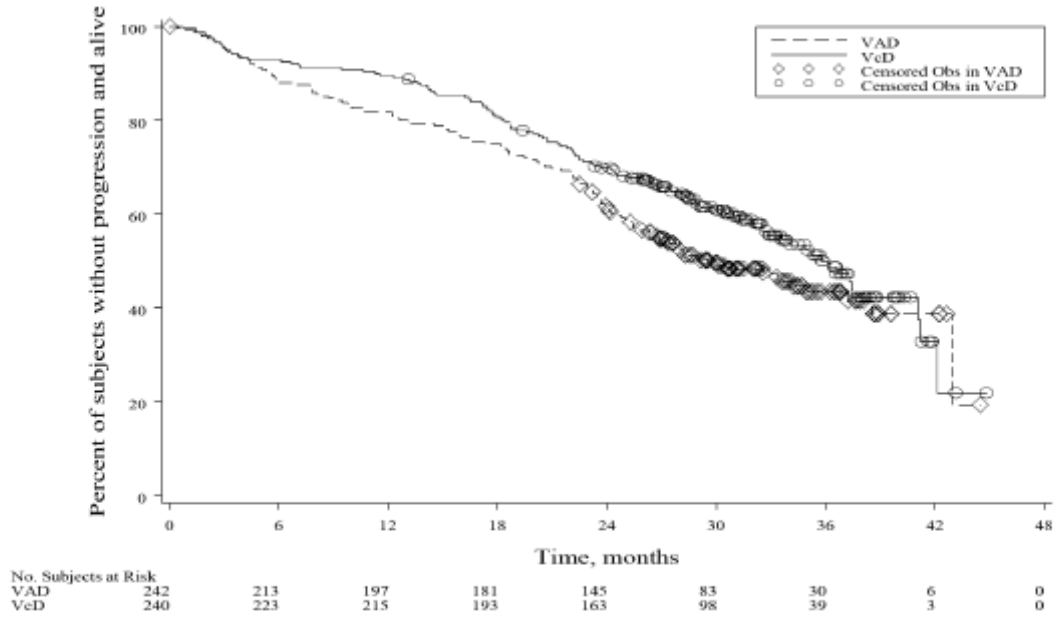
[b] HR for PFS, OS, and TTP based on a Cox's model stratified by beta2-microglobulin, Presence of chromosome 13; p-value by Log-rank test stratified by beta2-microglobulin, Presence of chromosome 13.

[c] Based on Kaplan-Meier product limit estimates.

Note: VAD includes Arms A1+A2 (VAD + VAD/DCEP); VcD includes Arms B1+B2 (VcD + VcD/DCEP)

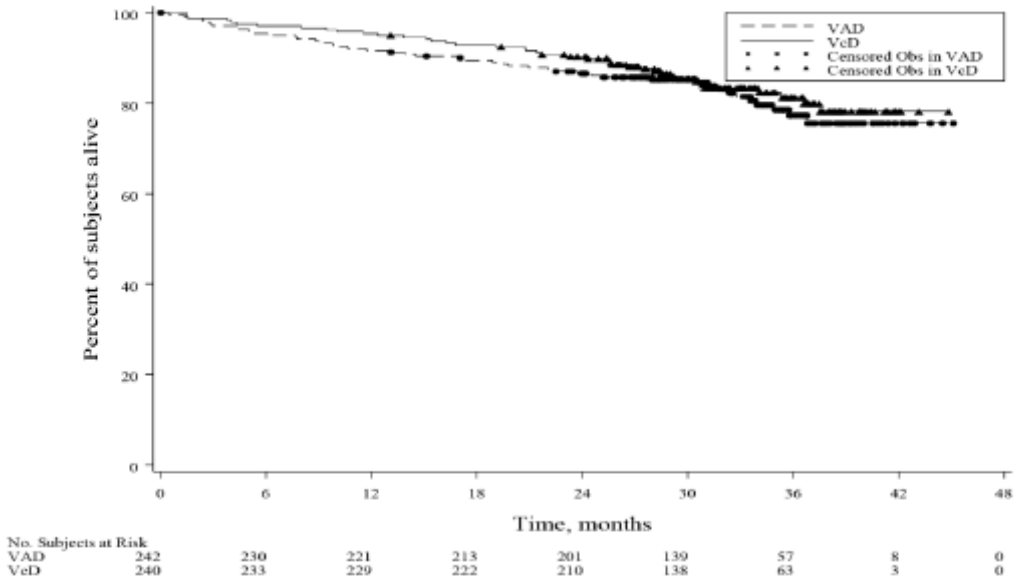
Note: A HR <1or OR>1 indicates an advantage for VcD.

Figure 8 – Kaplan-Meier Plot of Progression-Free Survival (Study IFM 2005-01 ITT analysis set)



VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcD=VELCADE, dexamethasone
Page 1 of 1 generated by fefsur02.sas

Figure 9 – Kaplan-Meier Plot of Overall Survival (Study IFM 2005-01 ITT analysis set)



VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcD=VELCADE, dexamethasone
Page 1 of 1 generated by fefsur05.sas

The values presented in the table below reflect the clinical database with respect to the number of subjects who received stem cell mobilization with granulocyte-colony stimulating factor (G-CSF), as well as the number of subjects who had stem cells collected.

Table 7 – Stem cell related procedures and transplant (Study IFM 2005-01)

(Study IFM 2005-01:Safety for Induction Analysis Set)

	-- VAD(A1+A2) -- (N=239)	-- VcD(B1+B2) -- (N=239)	------ Total ------ (N=478)
Subjects treated with stem cell mobilization therapy, n (%)			
N	218	228	446
Yes	213 (98)	222 (97)	435 (98)
No	5 (2)	6 (3)	11 (2)
Subjects with stem cells collected, n (%)			
N	218	228	446
Yes	216 (99)	226 (99)	442 (99)
No	2 (1)	2 (1)	4 (1)
Number of stem cells collections, n (%)			
N	216	226	442
1	189 (88)	169 (75)	358 (81)
2	27 (13)	57 (25)	84 (19)
Total number of CD34 cells collected(10^6/kg)			
N	216	226	442
Mean (SD)	9.60 (3.938)	8.59 (4.190)	9.08 (4.095)
Median	8.89	7.69	8.16
Range	(3.4;27.9)	(0.4;39.3)	(0.4;39.3)
High dose chemotherapy, n (%)			
N	216	226	442
None	18 (8)	18 (8)	36 (8)
Single course	146 (68)	166 (73)	312 (71)
Second course	52 (24)	42 (19)	94 (21)
Subjects with stem cells transplanted, n (%)			
N	216	226	442
0	18 (8)	18 (8)	36 (8)
1	146 (68)	166 (73)	312 (71)
2	52 (24)	42 (19)	94 (21)

VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcD=VELCADE, dexamethasone; A1=VAD only; A2=VAD plus DCEP; B1=VcD only; B2=VcD plus DCEP

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Ancillary analyses

Analyses relative to baseline stratification factors, demographic data (sex and age) and disease characteristics (ISS staging and cytogenetic abnormalities), Creatinine clearance (ml/min) (<60 versus ≥60) were performed for post-induction and post-transplant response rate and PFS.

The point estimate of the odds ratio was >1 for all subgroups for evaluation of post-induction and post-transplant CR/nCR response rate, which is consistent with the overall observation of treatment effect in favor of the VcD group over the VAD group.

With the exception of ISS Stage I, the point estimate of the hazard ratio for PFS was <1 for all subgroups, which is consistent with the overall observation of treatment effect in favor of the VcD group over the VAD group. For the cytogenetic classification “high risk”, stage II, renal impairment

according to CR/nCR endpoint, it seemed that VcD treatment performs better than in standard risk patients.

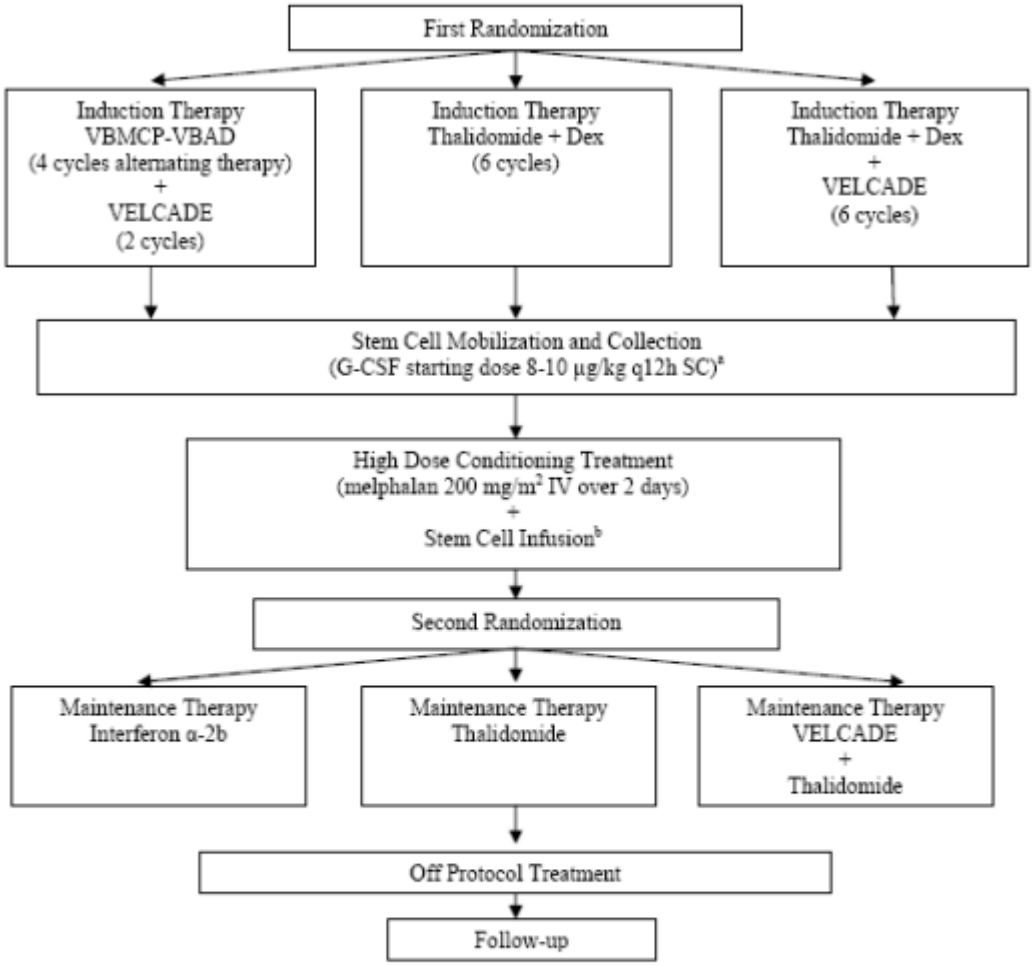
The results for other endpoints (post-induction response overall response rate, post-induction phase with induction intensification, post-transplant phase and post-transplant phase with induction intensification) were all consistent in favor of VcD treatment.

Study MMY-3010 (PETHEMA)

Methods

Study MMY-3010 was a Phase III, Open Label, Multicentre, Randomised, Comparative Study of VBMCP-VBAD/Velcade (vincristine, bis-chloronitrosourea, melphalan, cyclophosphamide, prednisone-vincristine, bis-chloronitrosourea, Adriamycin, dexamethasone/Velcade) versus Thalidomide/Dexamethasone (TD) versus Velcade/Thalidomide/Dexamethasone (VcTD) as Induction Therapy, Followed by High-Dose Chemotherapy with Autologous Haematopoietic Transplantation and Subsequent Maintenance Treatment with Interferon Alpha-2b versus Thalidomide versus Thalidomide/Velcade in Patients with Newly Diagnosed, Symptomatic Multiple Myeloma Aged 65 Years or Less.

Figure 10 – Study MMY-3010 design



AlloSCT=allogenic stem cell transplantation; G-CSF=granulocyte-colony stimulating factor; HDM=high-dose melphalan; HLA= human leukemia antigen haplotype; IV=intravenous(ly); SCT=stem cell transplant; VBAD=vincristine, bis-chloronitrosourea, Adriamycin, and dexamethasone; VBMCP=vincristine, bis-chloronitrosourea, melphalan, cyclophosphamide, and prednisone

[a] If stem cell mobilization failed, a second stem cell mobilization procedure including the use of high doses of cyclophosphamide followed by normal of pegylated G-CSF could have been performed.

[b] Subjects who did not achieve complete response (CR) following SCT and who had a HLA-identical donor could withdraw from the study to receive AlloSCT

Note: Since in the meta analysis the third arm VBMPC/VBAD was not considered, data referring to this arm were not extensively assessed.

Study participants

Key inclusion criteria for subject enrolment in the study were: age ≤65 years, eligible for autologous transplantation, with a life expectancy >3 months; diagnosis of symptomatic multiple myeloma and did not receive prior specific treatment for the disease with the exceptions of emergent steroid pulses prior to the start of induction treatment or bisphosphonate administration; measurable disease defined by the presence of quantifiable monoclonal component in serum, or in urine if light chain excretion was ≥200 mg/24 hours; ECOG performance status ≤2; laboratory values as specified in the study protocol; voluntarily signed an informed consent form; and able to comply with all study requirements.

Subjects meeting any of the following criteria were excluded from the study: had non-secretory multiple myeloma or previously received treatment for multiple myeloma, with the exceptions of emergent steroid pulses or bisphosphonate administration; had Grade 2 or higher peripheral neuropathy within 14 days of study entry; was scheduled for major surgery within 4 weeks of recruitment; had known hypersensitivity to any of the study treatments or their components; was currently in another clinical study or received an investigational agent within 30 days of study entry; experienced a myocardial infarction within 6 months of entry or had any cardiac deficiency as described in the protocol; was a carrier of the human immunodeficiency virus (HIV), hepatitis B virus surface antigen, or had active hepatitis C virus infection; or was pregnant or nursing.

Treatments

Enrolled subjects were randomised to receive 1 of 3 induction regimens TD, VcTD or VBMCP-VBAD/Vc for up to 6 cycles of induction treatment (4-week cycles=24 weeks), followed by stem cell mobilization, collection, and transplant. Eligible subjects underwent 1 SCT preceded by HDT with melphalan as conditioning treatment.

Three months after transplantation, subjects who continued on study were re-randomised to receive 1 of 3 maintenance treatments Interferon α-2b, Thalidomide or Velcade/thalidomide (VcT), which was continued for up to 3 years or until disease progression occurred. Subjects who did not achieve CR following auto-SCT and who had an identical HLA donor could withdraw from the study to receive allo-SCT. These subjects were not permitted to receive maintenance treatment as part of this study.

Objectives

The objective of this study was to compare the safety and efficacy of the 3 induction chemotherapy regimens. The study was also designed to compare the safety and efficacy of the 3 maintenance chemotherapy regimens.

Outcomes/endpoints

The primary efficacy endpoints were : post-induction and post-transplant response rates (CR+nCR+PR), post-induction and post-transplant CR+nCR rates. The final results for post-induction and post-transplant responses were centrally reviewed by the study principal investigator according to EBMT criteria (Bladé et al., 1998). Regular response evaluation was performed locally. A complete assessment of response was mandatory for all subjects at the end of induction treatment, 3 months after transplantation, and every 3 months during the maintenance and follow-up periods if there was no evidence of disease progression. However, a response using non-invasive procedures was performed on Day 1 of each new induction treatment cycle and also during maintenance treatment every month for the first year, every 2 months for 2 years, and every 3 months thereafter.

Secondary efficacy endpoints were PFS (the interval between the date of randomisation and the date of disease progression or death, whichever occurred first. Subjects who were progression-free and alive at the time of clinical cut-off were censored at the time of their last adequate disease assessment), OS and TTP.

Sample size

The sample size calculation was based on the assumption that a 2-sided α = 0.05, 80% power, and a 15% difference in the response rate between the different groups, with a subject recruitment period of

36 months and a scheduled analysis 12 months after the last subject was recruited, would require 390 subjects.

Randomisation

Subjects were randomly assigned to receive induction treatments in 1:1:1 ratio. Three months after transplantation, if no disease progression had occurred and the auto-SCT was complete and stable without unacceptable toxicity, the subjects were again randomly assigned to receive maintenance treatments in 1:1:1 ratio.

Blinding (masking)

Not applicable.

Statistical methods

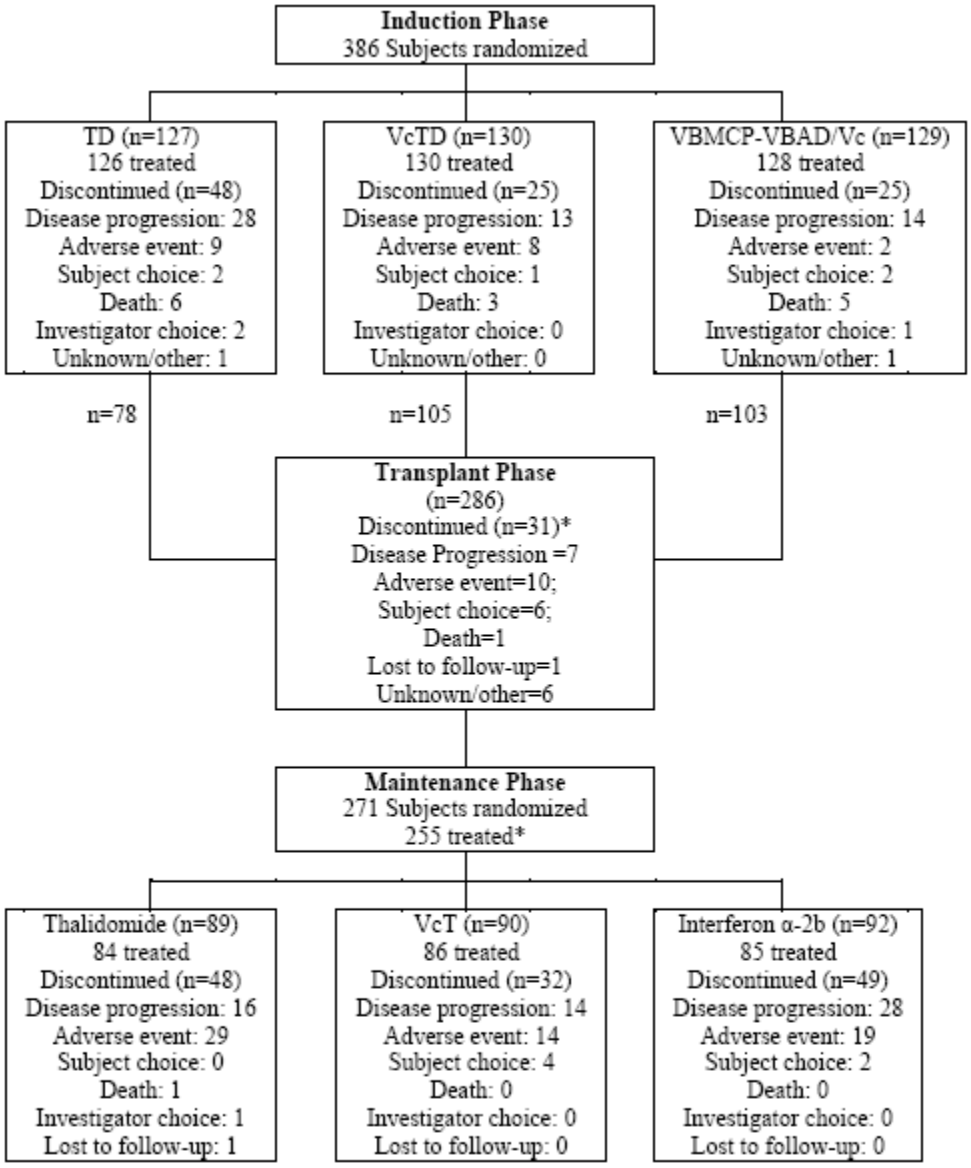
For the primary endpoint, post-induction and post-transplant response rate were summarized separately. Comparison of the response rate between the induction treatment groups was made using the Cochran-Mantel-Haenszel test. Response rate and the associated 95% confidence interval (CI) were provided for each treatment group. The CR/nCR rates post-induction and post-transplant were analysed similarly to response rate.

For the secondary endpoint, PFS, the log-rank test was used to compare the induction treatment groups and the maintenance treatment groups, respectively. The hazard ratio and its 95% CI for each pair of comparisons were estimated using the Cox regression procedure. Subgroup analysis for PFS was also provided. To adjust for confounding of maintenance therapy from 2-stage randomisation, inverseprobability weighting method was performed as an exploratory analysis to compare PFS of different induction therapies followed by the same maintenance therapy. Analyses similar to those used for PFS were used to assess the secondary endpoints overall survival and TTP.

Results

Participant flow

Figure 11 – Subject disposition in Study MMY-3010



* Discontinuations after transplant included those subjects who were randomized to maintenance treatment but may have discontinued before actually receiving maintenance treatment.
TD=thalidomide, dexamethasone; VcTD=VELCADE, thalidomide, dexamethasone;
VBMCP=vincristine, carmustine (BCNU), melphalan, cyclophosphamide, prednisone;
VBAD=vincristine, carmustine (BCNU), doxorubicin (Adriamycin), dexamethasone;
Vc=VELCADE ; VcT=VELCADE, thalidomide

The median duration of follow-up for all randomised subjects was 35.9 months (range: 0.9 to 61.1 months) and was consistent across Induction Phase treatment groups (TD: 36.4 months; VcTD: 35.4 months).

Recruitment

Study period: 09 April 2006 to 12 July 2011

Conduct of the study

There were 3 protocol amendments.

Baseline data

Demographic characteristics were well-balanced among the Induction Phase the treatment groups. The median age was 57 years in both groups (range: 25 to 65 years), with 62% of subjects ≥55 years of age. The majority of subjects were White (99%) and male (55%). Most subjects had an ECOG performance status of 0 (38%) or 1 (48%). The majority of subjects had myeloma of IgG (61%) or IgA (22%) subtype. Pre-induction ISS score was classified as Stage I for 38% of subjects, Stage II for 41%, and Stage III for 21%. Sixteen percent of subjects had creatinine clearance <60 mL/ml, while 84% had creatinine clearance <60 mL/min. The mean percent of plasma cells in the bone marrow was 39.8%. Forty-three percent of subjects had minor bone lesions, 32% had major lesions, and 25% had no lesions. The majority of subjects did not have osteopenia (65%) or extramedullary plasmacytomas (84%). Fifty percent of subjects were cytogenetically classified as standard risk; 13% were high risk. Demographic and baseline disease characteristics of subjects at the start of the Maintenance Phase were consistent across treatment groups and similar to those of the Induction Phase treatment groups at baseline.

Numbers analysed

Table 8 – Number of subjects per analysis set

(VELCADE Transplant Integrated Analysis of Efficacy: Intent-to-Treat Analysis Set)

	Non Vc-Based (N=785) n (%)	Vc-Based (N=787) n (%)	Total (N=1572) n (%)
Intent-to-Treat	785 (100)	787 (100)	1572 (100)
Evaluable	772 (98)	775 (98)	1547 (98)

Vc=VELCADE

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

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Outcomes and estimation

Results are presented in the table below.

Table 9 – Summary of key efficacy results (Study MMY-3010)

ITT Analysis Set	TD (N=127) % (95% CI)	VcTD (N=130) n (%) (95% CI)	OR (95% CI); p-value[a]
Post-induction response rate[b]			
CR	13.4 (8.0, 20.6)	35.4 (27.2, 44.2)	3.54 (1.90, 6.62); <0.001
CR+nCR	17.3 (11.2, 25.0)	49.2 (40.4, 58.1)	4.63 (2.61, 8.22); <0.001
Overall response (CR+nCR +PR)	61.4 (52.4, 69.9)	84.6 (77.2, 90.3)	3.46 (1.90, 6.27); <0.001
Post-transplant response rate[b]			
CR	23.6 (16.5, 32.0)	46.9 (38.1, 55.9)	2.86 (1.67, 4.88); <0.001
CR+nCR	34.6 (26.4, 43.6)	55.4 (46.4, 64.1)	2.34 (1.42, 3.87); 0.001
Overall response (CR+nCR+PR)	56.7 (47.6, 65.5)	77.7 (69.6, 84.5)	2.66 (1.55, 4.57); <0.001
			HR (95% CI); p-value[c]
Progression-free survival (mos)[d]			
Median (95% CI)	27.9 (19.8, 34.6)	55.5 (31.2, NE)	0.65 (0.45, 0.92); 0.015
1-year PFS rate	66.3 (57.3, 73.9)	81.9 (74.1, 87.6)	---
2-year PFS rate	55.0 (45.6, 63.3)	63.8 (54.7, 71.6)	---
3-year PFS rate	40.2 (30.6, 49.5)	55.2 (45.2, 64.1)	---
Overall survival (mos)[d]			
Median (95% CI)	NE (50.6, NE)	55.5 (55.5, NE)	0.80 (0.48, 1.34); 0.393
1-year OS rate	89.7 (82.9, 93.9)	91.5 (85.2, 95.2)	---
2-year OS rate	81.3 (73.2, 87.2)	85.9 (78.5, 90.9)	---
3-year OS rate	77.6 (68.6, 84.3)	81.1 (72.4, 87.3)	---
Time to progression (mos)[d]			
Median (95% CI)	29.0 (23.3, 45.9)	NE (31.9, NE)	0.64 (0.44, 0.93); 0.017
1-year TTP rate	69.4 (60.4, 76.8)	84.6 (76.9, 89.9)	---
2-year TTP rate	57.5 (48.0, 66.0)	65.7 (56.4, 73.5)	---
3-year TTP rate	42.1 (32.1, 51.7)	56.7 (46.3, 65.7)	---

CR=complete response; HR=hazard ratio; ITT=intent to treat; mos=months; nCR=near complete response; NE=not estimable; OR=odds ratio; OS=overall survival; PFS=progression-free survival; PR=partial response; TD=thalidomide, dexamethasone; VcTD=VELCADE, thalidomide, dexamethasone

[a] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio; p-values by Cochran Mantel-Haenszel chi-squared test.

[b] Response results were based on central review by the principal investigators.

[c] HR for PFS, OS, and TTP based on a Cox's model; p-value by Log-rank test.

[d] Based on Kaplan-Meier product limit estimates; includes Maintenance Phase treatment: interferon α-2b, thalidomide, or Vc+thalidomide.

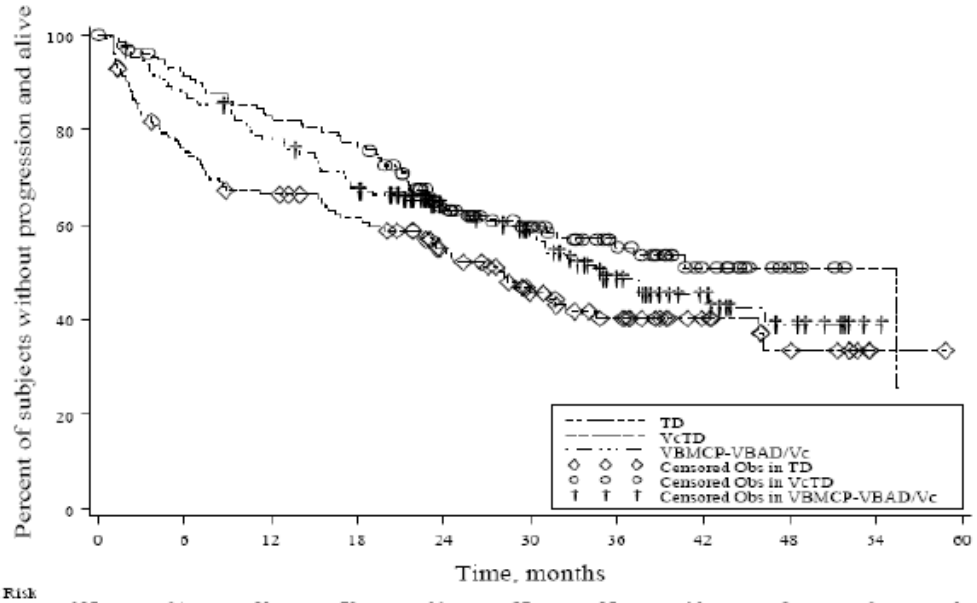
Note: A HR <1or OR>1 indicates an advantage for VcTD.

In Study MMY-3010, 75/130 (58%) subjects in the VcTD induction treatment group and 57/127 (45%) subjects in the TD induction treatment group were censored for determination of PFS. The types of censoring were similar for the 2 groups. Censoring for study cutoff occurred for 65 (87%) subjects in the VcTD induction treatment group and 44 (77%) subjects in the TD induction treatment group. Censoring for other reasons occurred for 10 (13%) subjects in the VcTD induction treatment group and 13 (23%) subjects in the TD induction treatment group.

Subjects only received a single course of SCT. On ITT population, 99% subjects in the TD treatment group and 97% subjects in the VcTD treatment group underwent a single SCT; the majority of SCTs were auto-SCT. The protocol allowed that subjects who did not achieve CR following HDT/SCT and who had an identical HLA donor could be withdrawn from the study at the investigator's discretion to receive allo-SCT. These subjects were ineligible to receive maintenance treatment. Although the study case report form did not explicitly identify allo-SCT as a potential reason for study discontinuation, 6 subjects (2 in the TD induction treatment group; 1 in the VcTD induction treatment group; 3 in the

VBMCP-VBAD/Vc induction treatment group) discontinued study treatment for unknown or other causes; this likely reflects the largest possible number of subjects who received allo-SCT.

Figure 12 – Kaplan-Meier Plot of Progression-Free Survival by Induction Treatment Group (Study MMY-3010 ITT analysis set)



No. Subjects at Risk											
TD	127	94	81	72	56	37	27	15	9	2	1
VcTD	130	116	104	98	67	48	33	17	7	2	1
VBMCP-VBAD/Vc	129	113	99	84	59	48	29	18	9	2	1

TD=thalidomide, dexamethasone; VcTD=VELCADE, thalidomide, dexamethasone
VBMCP=vincristine, carmustine (BCNU), melphalan, cyclophosphamide, prednisone
VBAD=vincristine, carmustine (BCNU), doxorubicin (Adriamycin), dexamethasone, Vc=VELCADE
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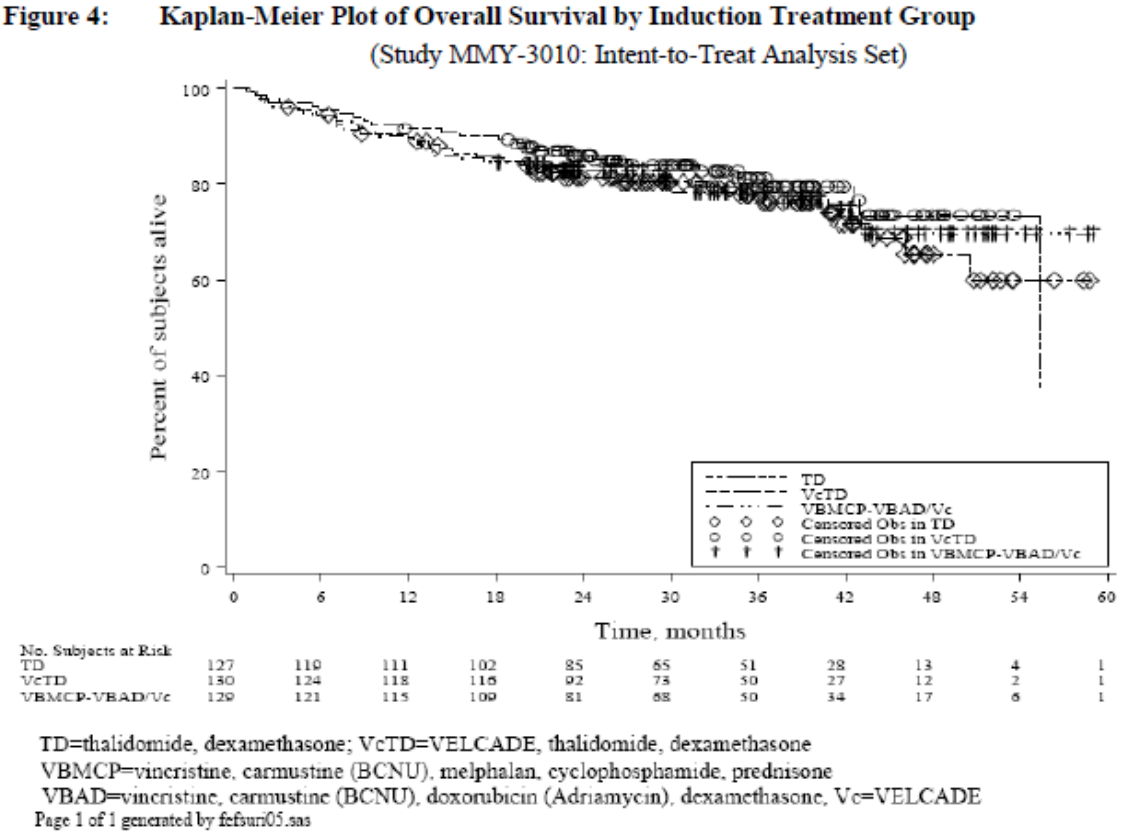
Figure 13 – Kaplan-Meier Plot of Overall Survival by Induction Treatment Group (Study MMY-3010 ITT analysis set)



Ancillary analyses

Analyses relative to baseline stratification factors, demographic data (sex and age) and disease characteristics (ISS staging and cytogenetic abnormalities), Creatinine clearance (mL/min) (<60 versus ≥60) were performed for post-induction and post-transplant response rate. As presented in the table below, results of the subgroups analysis were consistent with the overall observation of treatment effect in favour of the VcTD group over the TD group.

Summary of main studies

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 10 – Summary of Efficacy for trial 26866138-MMY-3003

Title: A Randomised Phase 3 Study on the Effect of Bortezomib Combined With Adriamycin, Dexamethasone (AD) for Induction Treatment, Followed by High-Dose Melphalan, and Bortezomib Alone During Maintenance in Patients With Multiple Myeloma	
Study identifier	26866138-MMY-3003 EudraCT Number: 2004-000944-26

Design	A randomised, open-label, multicentre, Phase 3 study in subjects with previously untreated Durie-Salmon Stage II or Stage III multiple myeloma. Study treatment occurred in 3 phases: induction treatment (including stem cell mobilization and collection), transplantation (including conditioning with HDM and stem cell infusion), and maintenance treatment.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		6 to 7 months Not applicable Up to 2 years
Hypothesis	Superiority		
Treatment groups	VAD		VAD induction treatment (up to three, 28-day cycles) with vincristine 0.4 mg/day IV Days 1 to 4, doxorubicin (Adriamycin) 9 mg/m^2 IV Days 1 to 4, and dexamethasone 40 mg/day PO Days 1 to 4, Days 9 to 12, and Days 17 to 20; followed by high-dose melphalan (100 mg/m^2/day for a total of 2 days IV); and maintenance treatment with thalidomide (50 mg/day PO) n=416
	VcAD		VcAD induction treatment (up to three, 28-day cycles) with Velcade 1.3 mg/m^2 IV Days 1, 4, 8, and 11, doxorubicin (Adriamycin) 9 mg/m^2 IV Days 1 to 4, and dexamethasone 40 mg/day PO Days 1 to 4, Days 9 to 12, and Days 17 to 20; followed by high-dose melphalan (100 mg/m^2/day for a total of 2 days IV); and maintenance treatment with Velcade (1.3 mg/m^2 once every 2 weeks IV). n=417
Endpoints and definitions	Primary endpoint	PFSC	Progression-free survival: the interval between the date of randomisation and the date of disease progression or death from any cause; whichever occurred first. Subjects who received allo-SCT before progression/relapse were censored at the date of transplantation.

	Secondary endpoint	Best response on protocol	Best post-induction response of the following categories: CR, nCR, VGPR, PR. ORR=(CR+nCR+VGPR+PR)
	Secondary endpoint	Post-induction response rate	Best post-induction response of the following categories: CR, near CR (nCR), VGPR, PR. ORR=(CR+nCR+VGPR+PR)
	Secondary endpoint	Post-transplant response rate	Best post-transplant response of the following categories: CR, near CR (nCR), VGPR, PR. ORR=(CR+nCR+VGPR+PR)
	Secondary endpoint	OS	Overall survival: the interval between the date of randomisation and the date of death from any cause.
	Secondary endpoint	PFS without censoring	PFS without censoring at allo-SCT: the interval between the date of randomisation and the date of disease progression or death from any cause, whichever occurred first
	Secondary endpoint	PFS from HDM	PFS from HDM: the interval between the date of last HDM administration and the date of disease progression or death from any cause, whichever occurred first for subjects who achieved at least PR on induction treatment, CAD, or HDM
	Other endpoint	TTP	Time-to-progression: similarly defined as PFS without censoring, except that death not due to progression would not be considered an event
	Other endpoint	Duration of CR	Duration of CR: For subjects with confirmed CR, duration of CR was defined as the time from the date of first documentation of a confirmed response to the date of first documented PD.
Database lock	Clinical cutoff in April 2011		

Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat Clinical cutoff in April 2011		
Descriptive statistics and estimate variability	Treatment group	VAD	VcAD
	Number of subjects	416	417

	PFSC (median months)	28.1	35.0
	95% CI	(24.8; 31.8)	(30.8; 39.2)
Effect estimate per comparison	Primary endpoint PFSC	Comparison groups	VcAD vs VAD
		Hazard Ratio	0.76
		95% CI	(0.63;0.91)
		P-value	0.003
Notes	Hazard ratio and p-value are based on stratified analyses.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat Clinical cutoff in April 2011		
Descriptive statistics and estimate variability	Treatment group	VAD	VcAD
	Number of subjects	416	417
	Best response on protocol (%)	CR: 26.7 CR+nCR: 37.3 CR+nCR+VGPR: 58.9 ORR: 85.1	CR: 36.2 CR+nCR: 50.1 CR+nCR+VGPR: 77.2 ORR: 91.4
	95% CI for %	CR: 22.5 - 31.2 CR+nCR: 32.6 - 42.1 CR+nCR+VGPR: 54.0 - 63.7 ORR: 81.3 - 88.4	CR: 31.6 - 41.0 CR+nCR: 45.2 - 55.0 CR+nCR+VGPR: 72.9 - 81.2 ORR: 88.2 - 93.9
	Post-induction response rate (%)	CR: 2.9 CR+nCR: 6.3 CR+nCR+VGPR: 19.5 ORR: 61.3	CR: 11.0 CR+nCR: 18.2 CR+nCR+VGPR: 50.1 ORR: 84.2
	95% CI for %	CR:: 1.5 - 5.0 CR+nCR: 4.1 - 9.0 CR+nCR+VGPR: 15.8 - 23.6 ORR: 56.4 - 66.0	CR:: 8.2 - 14.4 CR+nCR: 14.6 - 22.3 CR+nCR+VGPR: 45.2-55.0 ORR: 80.3 - 87.5
	Post-transplant response rate (%)	CR: 12.3 CR+nCR: 19.7 CR+nCR+VGPR: 38.9 ORR: 65.9	CR: 22.5 CR+nCR: 32.6 CR+nCR+VGPR: 57.8 ORR: 77.5
	95% CI for %	CR: 9.3 - 15.8 CR+nCR: 16.0 - 23.9 CR+nCR+VGPR: 34.2 - 43.8 ORR: 61.1 - 70.4	CR: 18.6 - 26.9 CR+nCR: 28.1 - 37.3 CR+nCR+VGPR: 52.9 - 62.6 ORR: 73.1 - 81.4
	OS (median months) 95% CI	Not estimable (NE) (59.9; NE)	Not estimable (NE) (63.9; NE)
	PFS without censoring (median months) 95% CI	28.6 (25.2; 31.8)	34.5 (30.7; 38.3)
	PFS from HDM (median months)	26.1	31.3

	95% CI	(22.1; 31.7)	(26.7; 33.9)
	TTP (median months) 95% CI	31.7 (27.4; 35.4)	37.4 (33.3; 39.8)
	Duration of CR (median months) 95% CI	30.1 (24.2; 37.5)	34.0 (25.8; 42.7)
Effect estimate per comparison	Secondary endpoint Best response on protocol	Comparison groups	VcAD vs. VAD
		Odds ratio	CR: 1.55 CR+nCR: 1.69 CR + nCR + VGPR: 2.37 ORR: 1.81
		95% CI	CR: (1.15,2.09) CR+nCR: (1.28,2.23) CR + nCR + VGPR: (1.75,3.21) ORR: (1.17,2.79)
		P-value	CR: 0.004 CR+nCR: <0.001 CR + nCR + VGPR: <0.001 ORR: 0.007
	Secondary endpoint Post-induction response rate	Comparison groups	VcAD vs. VAD
		Odds ratio	CR: 4.21 CR+nCR: 3.40 CR + nCR + VGPR: 4.16 ORR: 3.32
		95% CI	CR: (2.20,8.04) CR+nCR: (2.12,5.45) CR + nCR + VGPR: (3.05,5.68) ORR: (2.38,4.62)
		P-value	CR: <0.001 CR+nCR: <0.001 CR + nCR + VGPR: <0.001 ORR: <0.001
	Secondary endpoint Post-transplant response rate	Comparison groups	VcAD vs. VAD
		Odds ratio	CR: 2.11 CR+nCR: 2.00 CR + nCR + VGPR: 2.13 ORR: 1.74

		95% CI	CR: (1.45,3.08) CR+nCR: (1.45,2.76) CR + nCR + VGPR: (1.61,2.81) ORR: (1.28,2.36)
		P-value	CR: <0.001 CR+nCR: <0.001 CR + nCR + VGPR: <0.001 ORR: <0.001
	Secondary endpoint OS	Comparison groups	VcAD vs. VAD
		Hazard ratio	0.82
		95% CI	(0.63;1.05)
		P-value	0.120
	Secondary endpoint PFS without censoring	Comparison groups	VcAD vs. VAD
		Hazard ratio	0.80
		95% CI	(0.67;0.95)
		P-value	0.012
	Secondary endpoint PFS from HDM	Comparison groups	VcAD vs. VAD
		Hazard ratio	0.82
		95% CI	(0.67;1.00)
		P-value	0.052
	Other endpoint TTP	Comparison groups	VcAD vs. VAD
		Hazard ratio	0.79
		95% CI	(0.65;0.95)
		P-value	0.010
Notes	Hazard ratio or odds ratio and p-value are based on stratified analyses. PFS from HDM and duration of CR were analysed on a subset of the ITT population (please refer to endpoint definition for details).		

Table 11 – Summary of Efficacy for trial IFM 2005-01

Title: Open-Label, Multicentre, Randomised Phase 3 Study to Compare the Combination of Velcade® and Dexamethasone With VAD-Type Chemotherapy in the Treatment of Patients up to the Age of 65 With Newly Diagnosed Multiple Myeloma		
Study identifier	IFM 2005-01 EudraCT Number: 2005-000537-38	
Design	Randomised, open-label, multicentre, Phase 3 study that enrolled men and women up to the age of 65 years, inclusive, with previously untreated Durie-Salmon Stage II or III multiple myeloma or Durie-Salmon Stage I disease with symptomatic bone lesions. Study treatment included induction treatment or induction treatment plus induction intensification treatment, followed by stem cell mobilization, collection, and transplantation (including conditioning with high-dose melphalan.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	4 to 8 months not applicable not applicable

Hypothesis	Superiority		
Treatment groups	A1		VAD (vincristine 0.4 mg/day IV Days 1 to 4, doxorubicin (Adriamycin) 9 mg/m^2 IV Days 1 to 4, and dexamethasone 40 mg/day PO Days 1 to 4, 9 to 12 and 17 to 20 of Cycles 1 and 2, Days 1 to 4 of Cycles 3 and 4) n=121
	A2		VAD followed by induction intensification treatment with DCEP (dexamethasone 40 mg/day PO, cyclophosphamide 400 mg/m^2/day IV, etoposide or etoposide phosphate 40 mg/m^2/day IV, and cis-platinum 15 mg/m^2/day IV; Days 1 to 4) n=121
	B1		VcD (Velcade 1.3 mg/m^2 IV Days 1, 4, 8, and 11 and dexamethasone 40 mg/day PO Days 1 to 4, 9 to 12 and 17 to 20 of Cycles 1 and 2, Days 1 to 4 of Cycles 3 and 4) n=121
	B2		VcD followed by induction intensification treatment with DCEP n=119
Endpoints and definitions	Primary endpoint	Post-induction CR/nCR	Proportion of subjects who achieved a CR or nCR (including immunofixation + and -) following induction treatment with VAD (Treatment Groups A1+A2) or VcD combination induction treatment groups (Treatment Groups B1+B2).
	Secondary endpoint	Post-induction response	Proportion of subjects who achieved a CR, nCR, VGPR, or PR post-induction
	Secondary endpoint	Post-transplant response	Proportion of subjects who achieved a CR, nCR, VGPR, or PR post-transplant
	Secondary endpoint	Post-transplant CR/nCR	Post-transplant CR/nCR rate to be analysed similarly to the primary endpoint (post-induction CR/nCR rate)
	Secondary endpoint	PFS	Progression-free survival: the interval between the date of randomisation and the date of disease progression or death from any cause, whichever occurred first
	Secondary endpoint	OS	Overall survival: the interval between the date of randomisation and the date of death from any cause
	Secondary endpoint	TTP	Time to disease progression: the interval between the date of randomisation and the date of disease progression or death due to disease progression, whichever occurred first

Database lock	Study completed in June 2009		
Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat Study completed in June 2009		
Descriptive statistics and estimate variability	Treatment group	VAD (A1+A2)	VcD (B1+B2)
	Number of subjects	242	240
	Post-induction CR/nCR (%)	6.2	14.6
	95% CI for %	3.5 - 10.0	10.4 - 19.7
Effect estimate per comparison	Primary endpoint Post-induction CR/nCR	Comparison groups	VcD (B1+B2) vs. VAD (A1+A2)
		Odds ratio	2.58
		95% CI	(1.37,4.85)
		P-value	0.003
Notes	The odds ratio and p-value are based on stratified analyses.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat Study completed in June 2009		
Descriptive statistics and estimate variability	Treatment group	VAD (A1+A2)	VcD (B1+B2)
	Number of subjects	242	240
	Post-induction response (%)	CR: 1.2 CR+nCR+VGPR: 14.9 ORR: 60.7	CR: 5.4 CR+nCR+VGPR: 37.1 ORR: 77.1
	95% CI for %	CR: 0.3 - 3.6 CR+nCR+VGPR: 10.6-20.0 ORR: 54.3 - 66.9	CR: 2.9 - 9.1 CR+nCR+VGPR: 31.0 - 43.5 ORR: 71.2 - 82.2
	Post-transplant response (%)	CR: 10.3 CR+nCR+VGPR: 45.0 ORR: 74.4	CR: 18.3 CR+nCR+VGPR: 62.5 ORR: 79.6
	95% CI for %	CR: 6.8 - 14.9 CR+nCR+VGPR: 38.7 - 51.5 ORR: 68.4 - 79.8	CR: 13.6 - 23.8 CR+nCR+VGPR: 56.0 - 68.6 ORR: 73.9 - 84.5
	Post-transplant CR/nCR (%)	23.1	37.5
	95% CI for %	18.0 - 29.0	31.4 - 44.0
	PFS (months)	29.7	36.1
	95% CI	(26.3; 37.2)	(32.5; 41.1)
	OS (months)	Not estimable (NE)	NE
	95% CI	NE, NE	NE, NE

	TTP (months)	30.6	37.3
	95% CI	(27.2; 38.5)	(33.6; 41.2)
Effect estimate per comparison	Secondary endpoint Post-induction response	Comparison groups	VcD (B1+B2) vs. VAD (A1+A2)
		Odds ratio	CR: 4.71 CR+nCR+VGPR: 3.36 ORR: 2.18
		95% CI	CR: (1.31,16.93) CR+nCR+VGPR: (2.16,5.21) ORR: (1.46,3.24)
		P-value	CR: 0.010 CR+nCR+VGPR: <0.001 ORR: <0.001
	Secondary endpoint Post-transplant response	Comparison groups	VcD (B1+B2) vs. VAD (A1+A2)
		Odds ratio	CR: 1.95 CR+nCR+VGPR: 2.04 ORR: 1.34
		95% CI	CR: (1.15,3.29) CR+nCR+VGPR: (1.42,2.94) ORR: (0.87,2.05)
		P-value	CR: 0.011 CR+nCR+VGPR: <0.001 ORR: 0.179
	Secondary endpoint Post-transplant CR/nCR	Comparison groups	VcD (B1+B2) vs. VAD (A1+A2)
		Odds ratio	1.98
		95% CI	(1.33,2.95)
		P-value	0.001
	Secondary endpoint PFS	Comparison groups	VcD (B1+B2) vs. VAD (A1+A2)
		Hazard ratio	0.78
		95% CI	(0.60;1.01)
		P-value	0.058
	Secondary endpoint OS	Comparison groups	VcD (B1+B2) vs. VAD (A1+A2)
		Hazard ratio	0.88
		95% CI	(0.58;1.35)
		P-value	0.561
	Secondary endpoint TTP	Comparison groups	VcD (B1+B2) vs. VAD (A1+A2)
		Hazard ratio	0.78
		95% CI	(0.60;1.02)
		P-value	0.069
Notes	The odds ratio or hazard ratio and p-value are based on stratified analyses.		

Table 12 – Summary of Efficacy for trial 26866138-MMY-3010

Title: A Phase III National, Open Label, Multicentre, Randomised, Comparative Study of VBMCP-VBAD/Velcade® versus Thalidomide/Dexamethasone versus Velcade/Thalidomide/Dexamethasone as Induction Therapy, Followed by High-Dose Chemotherapy with Autologous Haematopoietic Transplantation and Subsequent Maintenance Treatment with Interferon Alpha-2b versus Thalidomide versus Thalidomide/Velcade in Patients with Newly Diagnosed, Symptomatic Multiple Myeloma Aged 65 Years or Less		
Study identifier	26866138-MMY-3010 EudraCT Number: 2005-001110-41	
Design	Randomised, open-label, multicentre, Phase 3 study of men and women up to age 65 years, inclusive, with newly diagnosed, symptomatic, and previously untreated multiple myeloma. Study treatment occurred in 3 phases: induction treatment (including stem cell mobilization and collection), transplantation (including conditioning with HDM and stem cell infusion), and maintenance treatment. Three months post-transplantation, subjects were re-randomised (irrespective of induction regimen) to receive one of 3 maintenance therapies.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	24 weeks induction followed by auto-SCT Not applicable Up to 3 years maintenance treatment
Hypothesis	Superiority	
Treatment groups	Induction treatment: VBMCP-VBAD-Vc	VBMCP-VBAD (vincristine 0.03 mg/kg IV, maximum 2 mg; bis-chloronitrosourea 0.5 mg/kg IV; melphalan 0.25 mg/kg PO; cyclophosphamide 10 mg/kg IV; and prednisone 1 mg/kg/day PO Days 1 to 4, 0.5 mg/kg/day Days 5 to 8, and 0.25 mg/kg/day Days 9 to 12 - vincristine 1 mg IV, bis-chloronitrosourea 30 mg/m^2 IV, doxorubicin (Adriamycin) 40 mg/m^2 IV, and dexamethasone 40 mg/day PO) and Velcade (1.3 mg/m^2 IV) n=129
	Induction treatment: TD	Thalidomide (50, 100, and 200 mg PO) and dexamethasone (40 mg/day PO) n=127
	Induction treatment: VcTD	Velcade (1.3 mg/m^2 IV), thalidomide (50, 100, and 200 mg PO), and dexamethasone (40 mg/day PO) n=130
	Maintenance Treatment 1	Interferon α−2b (1.5 MU, 3 times a week) n=92
	Maintenance Treatment 2	Thalidomide (100 mg/day PO) n=89

	Maintenance Treatment 3		Velcade (1.3 mg/m^2 IV on Days 1, 4, 8, and 11 every 3 month cycle) and thalidomide (100 mg/day PO) n=90
Endpoints and definitions	Co-Primary endpoint	Post-induction, Post-transplant response rate	Proportion of subjects who achieved a response of CR, nCR, or PR. The response rates post-induction and post-transplant were summarized separately.
	Co-Primary endpoint	CR/nCR rates post-induction and post-transplant	Proportion of subjects who achieved a CR or nCR.
	Secondary endpoint	PFS	Progression-free survival: the interval between the date of randomisation and the date of disease progression or death, whichever occurred first.
	Secondary endpoint	OS	Overall survival: the interval between the date of randomisation and the subject's death from any cause
	Secondary endpoint	TTP	Time to progression: defined similarly to PFS except that death not due to progression was not considered an event.
Database lock	Clinical cutoff in July 2011		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Intent-to-treat Clinical cutoff in July 2011			
Descriptive statistics and estimate variability	Treatment group	TD	VcTD	VBMCP-VBAD
	Number of subjects	127	130	129
	Post-induction, Post-transplant response rate (%)	Post-induction CR: 13.4 ORR: 61.4 Post-transplant CR: 23.6 ORR: 56.7	Post-induction CR: 35.4 ORR: 84.6 Post-transplant CR: 46.9 ORR: 77.7	Post-induction CR: 20.2 ORR: 74.4 Post-transplant CR: 37.2 ORR: 76.0
	95% CI for %	Post-induction CR: 8.0 - 20.6 ORR: 52.4-69.9 Post-transplant CR: 16.5 - 32.0 ORR: 47.6-65.5	Post-induction CR: 27.2 - 44.2 ORR: 77.2 - 90.3 Post-transplant CR: 38.1 - 55.9 ORR: 69.6 - 84.5	Post-induction CR: 13.6 - 28.1 ORR: 66.0 - 81.7 Post-transplant CR: 28.9 - 46.2 ORR: 67.7 - 83.1

	CR/nCR rates post-induction and post-transplant (%)	Post-induction CR+nCR: 17.3 Post-transplant CR+nCR: 34.6	Post-induction CR+nCR: 49.2 Post-transplant CR+nCR: 55.4	Post-induction CR+nCR: 26.4 Post-transplant CR+nCR: 45.7
	95% CI for %	Post-induction CR+nCR: 11.2 - 25.0 Post-transplant CR+nCR: 26.4- 43.6	Post-induction CR+nCR: 40.4 - 58.1 Post-transplant CR+nCR: 46.4 - 64.1	Post-induction CR+nCR: 19.0 - 34.8 Post-transplant CR+nCR: 36.9 - 54.7
Effect estimate per comparison	Post-induction, Post-transplant response rate	Comparison groups	VcTD vs TD	
		Odds ratio	Post-induction CR: 3.54 ORR: 3.46 Post-transplant CR: 2.86 ORR: 2.66	
		95% CI	Post-induction CR: (1.90,6.62) ORR: (1.90,6.27) Post-transplant CR: (1.67,4.88) ORR: (1.55,4.57)	
		P-value	Post-induction CR: <.001 ORR: <.001 Post-transplant CR: <.001 ORR: <.001	
	CR/nCR rates post-induction and post-transplant	Comparison groups	VcTD vs TD	
		Odds ratio	Post-induction CR+nCR: 4.63 Post-transplant CR+nCR: 2.34	
		95% CI	Post-induction CR+nCR: (2.61,8.22) Post-transplant CR+nCR: (1.42,3.87)	
		P-value	Post-induction CR+nCR: <.001 Post-transplant CR+nCR: 0.001	
Notes	Effect estimates shown only for VcTD vs ID treatment groups. Odds ratio and p-value are based on un-stratified analyses.			
Analysis description	**Secondary analysis**			

Analysis population and time point description	Intent-to-treat Clinical cutoff in July 2011			
Descriptive statistics and estimate variability	Treatment group	TD	VcTD	VBMCP-VBAD
	Number of subjects	127	130	129
	PFS (median months)	27.9	55.5	34.9
	95% CI	(19.8; 34.6)	(31.2; NE)	(29.0; NE)
	OS (median months)	NE	55.5	NE
	95% CI	(50.6; NE)	(55.5; NE)	(NE ; NE)
	TTP (median months)	29.0	NE	37.5
	95% CI	(23.3; 45.9)	(31.9; NE)	(31.0; NE)
Effect estimate per comparison	Secondary endpoint PFS	Comparison groups	VcTD vs TD	
		Hazard ratio	0.65	
		95% CI	(0.45;0.92)	
		P-value	0.015	
	Secondary endpoint OS	Comparison groups	VcTD vs TD	
		Hazard ratio	0.80	
		95% CI	(0.48 ; 1.34)	
		P-value	0.393	
	Secondary endpoint TTP	Comparison groups	VcTD vs TD	
		Hazard ratio	0.64	
		95% CI	(0.44 ; 0.93)	
		P-value	0.017	
Notes	Effect estimates shown only for TD vs VcTD treatment groups NE = not estimable. Hazard ratio and p-value are based on un-stratified analyses.			

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

Methods

The integrated analysis performed by the MAH combined all subject-level data from 3 of the cooperative group studies (MMY-3003, IFM 2005-01, and MMY-3010), with the exception of the VBMCP-VBAD/Vc induction treatment group of Study MMY-3010; for the key efficacy endpoints, published results from study MMY-3006 were incorporated using meta-analytical methods.

Sensitivity analyses to demonstrate robustness of the findings were performed for the following subgroups (all tests were 2-sided): Age (<55 versus ≥55); Sex (male versus female); ISS stage (I versus II versus III); Cytogenetics classification (high risk, standard risk, not done); Renal function category (creatinine clearance <60 mL/min versus >60 mL/min). For each efficacy endpoint, the significance level was 0.05. Results of the subgroup analysis for the primary endpoint (CR+nCR) were provided in a Forest plot.

The 4 studies were comparable in terms of design (randomised, open-label, multicentre) with similar patient populations (men and women, up to 65 years of age with previously untreated multiple myeloma [Durie-Salmon stage II or III] and ECOG-equivalent performance status of 0 to 2/3). However, there was a lower percentage of subjects in Study MMY-3010 with cytogenetic high-risk (13% in ITT population, 16% TD and 12% VcTD) compared with those in Studies MMY-3003 (376 of 833 subjects; 45%) and IFM 2005-01 (226 of 470 subjects; 48%).

Each study met its primary endpoints with satisfactorily statistical significance levels. Consistent results were obtained for subgroup analyses within each study and regarding the induction regimens among studies.

Dexamethasone was included in all arms (Vc-based and non-Vc-based) in all studies. The number of cycles and duration of each cycle, were different across studies. The number of planned SCTs was 1 in Study MMY-3010, 1 or 2 in Studies MMY-3003 and IFM 2005-01, and 2 in Study MMY-3006.

With the exception of Study IFM 2005-01, all studies included maintenance/consolidation treatment, with 1 group receiving a Vc-based regimen. Studies MMY-3003 and MMY-3006 used Velcade maintenance/consolidation treatment exclusively for subjects who received Vc-based induction, while Study MMY-3010 re-randomised subjects to different maintenance treatment regardless of their induction treatment group.

Heterogeneity for confirming the external validity of the pooled results (e.g. subjects enrolled in studies are representative for the common target population, the extent of differences among studies of dosage schedule, treatment duration, sample size), was controlled by calculating the I-square for CR+nCR rate, PFS, and OS. An I-square of 0% indicates no heterogeneity observed, while larger values suggest increasing heterogeneity.

While the primary endpoints were different among the 3 studies, post-transplant CR/nCR rate was chosen as the primary endpoint for the integrated analysis since it is less susceptible, compared to PFS, to confounding effects of therapies administered after the end of the induction therapy (consolidation and maintenance therapies).

Results

CR+nCR

Results of the *post-induction* response rates are presented below.

Table 13 – Post-induction Response Rate

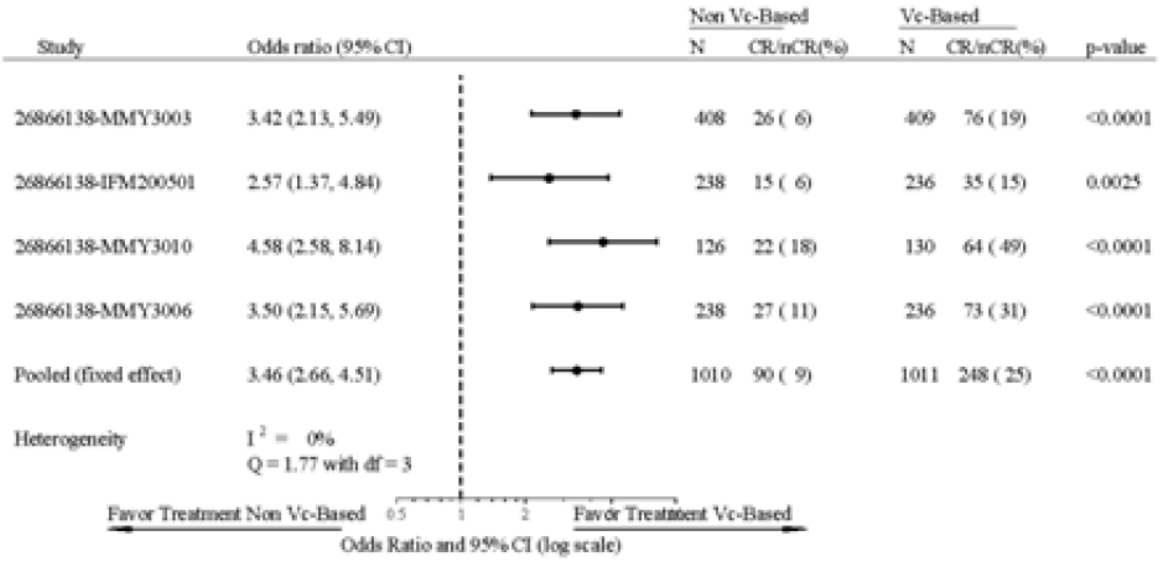
(VELCADE Transplant Integrated Analysis of Efficacy: Evaluable Analysis Set)

	-- Non Vc-Based (N=772) --			-- Vc-Based (N=775) --				
Category	n	%	95% CI for %	n	%	95% CI for %	Odds Ratio[a]	p-value[b]
Complete Response (CR)	32	4	3 - 6	105	14	11 - 16	3.92 (2.57,6.00)	<0.0001
Near CR (nCR)	31	4	3 - 6	70	9	7 - 11		
CR + nCR	63	8	6 - 10	175	23	20 - 26	3.45 (2.52,4.72)	<0.0001
Very good partial response (VGPR)	76	10	8 - 12	187	24	21 - 27		
CR + nCR + VGPR	139	18	15 - 21	362	47	43 - 50	4.03 (3.19,5.08)	<0.0001
Partial response (PR)	341	44	41 - 48	284	37	33 - 40		
Overall response rate (CR+nCR+VGPR+PR)	480	62	59 - 66	646	83	81 - 86	3.05 (2.40,3.87)	<0.0001
Minimal response (MR)	109	14	12 - 17	35	5	3 - 6		
No change	76	10	8 - 12	29	4	3 - 5		
Progressive Disease (PD)	55	7	5 - 9	24	3	2 - 5		
Not evaluable	50	6	5 - 8	38	5	3 - 7		

Vc=VELCADE
[a] Cochran-Mantel-Haenszel estimate stratified by study
[b] P-value from the Cochran Mantel-Haenszel chi-squared test.
Note: VGPR is not reported as a response category for Study MMY-3010.
An odds ratio greater than 1 favors the Vc-based treatment group.

Figure 14 – Post-induction CR/nCR Response Rate: Forest Plot of individual studies and integrated data including study MMY-3006

(VELCADE Transplant Integrated Analysis of Efficacy: Evaluable Analysis Set

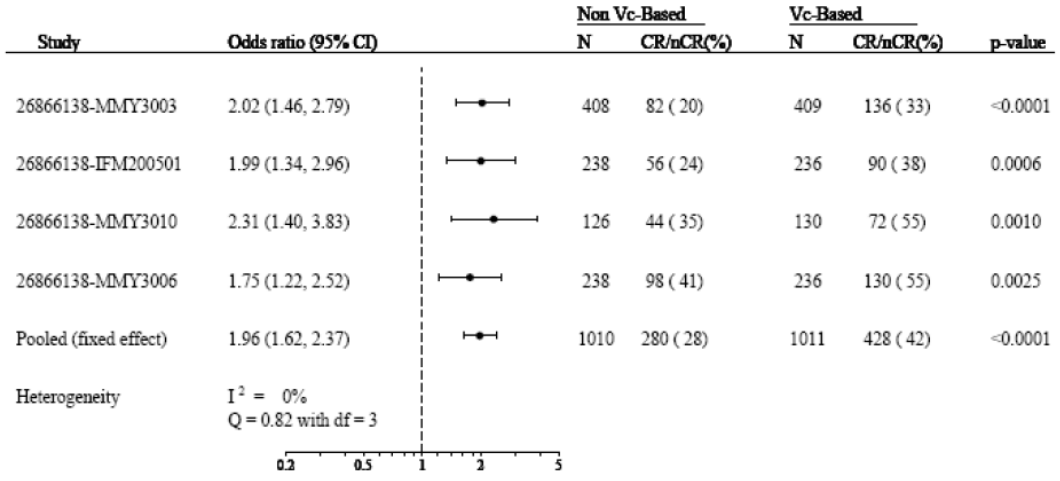


CR=complete response; nCR=near complete response; Vc=VELCADE
An odds ratio greater than 1 favors the Vc-based group.
Study MMY-3006: source=Cavo et. al. (2010).
Generated by fefrsp07b.sas

Results of the *post-transplant* CR/nCR rate are presented below.

Figure 15 – Post-Transplant CR/nCR Response Rate: Forest Plot of individual studies and integrated data including study MMY-3006

(VELCADE Transplant Integrated Analysis of Efficacy: Evaluable Analysis Set)



CR=complete response; nCR=near complete response; Vc=VELCADE
An odds ratio greater than 1 favors the Vc-based group.
Study MMY-3006: source=Cavo et. al. (2010).

Consistent with what was observed in the single studies, the post-induction and post-transplant CR+nCR rates were significantly improved with Vc-based induction treatment in all subgroups of subjects defined by age, sex, ISS stage, cytogenetics classification, and renal function.

Stem Cell-Related Procedures and Transplant

For the integrated data, 1,353 of 1,572 (86%) randomised subjects had stem cells collected; 656 (84%) subjects in the non-Velcade-based induction group and 697 (89%) subjects in the Velcade-based induction group.

Of the subjects with stem cells collected, 624 (95%) subjects in the non-Velcade-based induction group and 667 (96%) subjects in the Velcade-based induction group underwent transplantation. Similar percentages of subjects in the non-Velcade-based and Velcade-based induction groups underwent a single transplant procedure (70% versus 72%, respectively).

Table 14 – Stem cell transplant related procedures

(VELCADE Transplant Integrated Analysis of Efficacy: Intent-to-Treat Analysis Set)

	- Non Vc-Based - (N=785)	---- Vc-Based --- (N=787)	----- Total ----- (N=1572)
Subjects treated with stem cell mobilization therapy, n (%)[a]			
N	707	724	1431
Yes	653 (92)	696 (96)	1349 (94)
No	54 (8)	28 (4)	82 (6)
Subjects with stem cells collected, n (%)			
N	707	724	1431
Yes	656 (93)	697 (96)	1353 (95)
No	51 (7)	27 (4)	78 (5)
Number of stem cell collections, n (%)			
N	656	697	1353
1	613 (93)	626 (90)	1239 (92)
2	43 (7)	71 (10)	114 (8)
Total number of CD34 cells (10^6/kg) collected			
N	648	688	1336
Mean (SD)	10.23 (6.627)	10.15 (7.170)	10.19 (6.909)
Median	9.00	8.33	8.60
Range	(1.7;60.0)	(0.4;56.8)	(0.4;60.0)
Subjects treated with high dose chemotherapy[b], n (%)			
N	545	560	1105
Yes	545 (100)	560 (100)	1105 (100)
Number of stem cell transplants, n (%)			
N	624	667	1291
1	438 (70)	483 (72)	921 (71)
2	186 (30)	184 (28)	370 (29)

Vc=VELCADE

[a] Information regarding stem cell mobilization therapy was missing for 4 subjects in Study IFM 2005-01.

[b] High dose chemotherapy information was not collected in study MMY-3010.

Clinical studies in special populations

No dedicated study was performed in special population.

Supportive study: Study MMY-3006 (GIMEMA)

Methods

This study refers to published data (Cavo et al. 2010) with no subject level data are available. The cut off date was 30 June 2010.

The Primary efficacy endpoint was post induction CR+nCR. Secondary efficacy endpoints were post transplant CR+nCR, TTP or time to relapse, PFS, and OS.

Due to the exclusive use of Velcade-based consolidation treatment in subjects who received Velcade-based induction treatment, it was not possible to separate out the effects between induction and consolidation treatment on long-term outcomes; i.e., PFS and OS.

Results

The median duration of follow-up from the start of study treatment was 36 months.

Over the ITT population, 44% in VTD and 32.5% in TD received the first transplant; about 35% in both arms underwent the second transplant.

A high % of discontinuation was observed in the TD arm (8% of the enrolled population) vs the VcTD arm (4% of the enrolled population) before completing 3 induction cycles treatment. However, in the post-transplant phase for the first transplant, the highest discontinuation % was reported in the VcTD arm (10% of the enrolled population) vs the TD arm (6% of the enrolled population). After the second transplantation, still a higher % of discontinuation was observed in the VcTD arm (5% vs 3% of the enrolled population in the VcTD and TD arms, respectively).

Overall, out of the ITT population, 27% in VcTD arm and 24% in the TD arm completed the treatment.

The HR for PFS was 0.63 (95% CI: 0.45, 0.88; p=0.0061).

The estimated 3-year survival rate was similar in both arms: 84% in the TD treatment group and 86% in the VcTD treatment group.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The present application was based on three phase 3 studies, 1 supportive study and a meta-analysis.

All studies were randomised, open-label, multicentre carried out by cooperative groups with the objective to compare the efficacy and safety of Velcade-based regimen vs non-Velcade-based regimen.

A number of differences in the design of these studies were observed (heterogeneity of treatments associated with Velcade or number of cycles across studies, differences in maintenance/consolidation treatments, percentage of subjects with high-risk cytogenetics).

The presented meta-analysis was well-designed. The statistical analyses were correct and supported the efficacy for Vc-based induction regimen in transplant-eligible subjects with newly diagnosed multiple myeloma.

While the primary endpoints were different among the 4 studies, the endpoint CR+nrCR was selected in the integrated analysis since it is less susceptible, compared to PFS, to confounding effects of therapies administered after the end of the induction therapy (consolidation and maintenance therapies).

Efficacy data and additional analyses

The integrated analyses showed statistically and clinicallysignificant differences in CR/nCR rate for the Velcade-based induction therapies compared with the non-Velcade-based induction therapies. This finding was consistent with the results of all individual studies which all met their primary endpoints with consistent results across clinically relevant patient subgroups.

Although overall the efficacy of these different combinations seemed similar, a sound comparison of the benefit of Velcade-based combination therapies among the 3 studies was challenging as it was confounded by too many variables to allow to draw any firm conclusions.

No new dose-finding study to support the proposed posology (dose, number of cycles, duration of cycles) for Velcade in the new indication as induction for SCT eligible patients was performed. The starting dose of Velcade 1,3 mg/m^2 was chosen according to the currently approved Velcade dose for treatment of patients with previously untreated multiple myeloma in combination with other agents (that also applies to the monotherapy regimen in patients who have received at least 1 prior therapy), which was acceptable.

In studies MMY-3003 (VAD vs VcAD) and MMY-3006 (TD vs VcTD) 3 cycles were foreseen of 28 and 21 days, respectively; in study IFM-2005-01 (VAD vs VcD) there were 4 cycles of 21 days, and in study MMY-3010 (TD vs VcTD) the cycles were 6 of 28 days; this represents a major limitation on the comparability of the results since the intensity of the treatment might differently affect the efficacy.

Based on the evidence of efficacy from the results of these studies, the CHMP considered that the posology recommendations for the VcTD combination should be four 28-day cycles, followed by 2 additional cycles in patients with at least partial responses (see also section on clinical safety).

Dexamethasone was included in all arms (Vc-based and non-Vc-based) in all studies and therefore the combination of dexamethasone should be reflected in section 4.1 of the SmPC.

The VcAD combination regimen showed similar quality of post-induction and post-transplant response but safety concerns were identified (see section on clinical safety).

2.4.4. Conclusions on the clinical efficacy

Overall efficacy data showed a consistent benefit associated with Vc-based therapy compared to non Vc-based therapies in the first line induction treatment of MM in patients eligible for SCT. The primary efficacy end-points were met in all these studies.

2.5. Clinical safety

Patient exposure

The safety database presented in support of the present extension of indication, included safety data collected from the three Phase 3 clinical studies (MMY-3003, IFM 2005-01, and MMY-3010). Data from single studies were pooled and the MAH compared the safety data from the Velcade-based induction regimen (i.e., VcAD, VcD, and VcTD treatment groups) versus non-Velcade-based induction regimen (ie, VAD and TD treatment groups).

Integrated safety analysis set (N=1,555) comprised only Pooled Induction Phase data from Studies MMY-3003 (n=821), IFM 2005-01 (n=478), and MMY-3010 (n=256).

The median number of cycles of induction treatment administered in Studies MMY-3003, IFM 2005-01, and MMY-3010 were 3, 4, and 6 cycles, respectively. The median treatment duration was 11.43 months in non-Vc-based vs 11.00 months Vc-based.

During the Induction Phase, the median dose intensity of Velcade ranged from 5.10 mg/m^2/cycle to 5.20 mg/m^2/cycle across all 3 Phase 3 studies. During the Maintenance Phase, the median dose

intensity of Velcade was 0.48 mg/m^2/week for Study MMY-3003 and 1.61 mg/m^2/month for Study MMY-3010.

During induction treatment, the median total dose (1,440.0 mg), the median dose intensity (480.0 mg/cycle), and the median relative dose intensity (100%) of dexamethasone were the same in both the non-Velcade-based and Velcade-based groups.

This safety assessment mainly pertained to the induction phase.

Adverse events

Study MMY-3003 (VAD vs VcAD)

Eight hundred twenty one (99%) subjects were included in the Induction Phase safety analysis set and 699 (84%) subjects in the Transplant Phase safety analysis set (76% of subjects received HDM/auto-SCT, and 7% of subjects received allo-SCT).

During the Induction Phase, while the overall % adverse events and drug-related adverse events were balanced among the VcAD and VAD treatment groups, there was a higher frequency of serious adverse events (53% and 40%, respectively), drug-related serious adverse events (43% and 28%, respectively), Grade >3 adverse events (79% and 72%, respectively), and drug-related Grade $\geq$ 3 adverse events (70% and 61%, respectively) in the VcAD treatment group than in the VAD treatment group.

Among AEs reported in at least 10% of subjects, AEs reported more in the VcAD group than in the VAD group included peripheral neuropathy, peripheral sensory neuropathy, neuralgia, infections (Herpes Zoster), nausea and thrombocytopenia. However, the overall rate of nervous system disorders was high in the VcAD group: 65%. The rate of neuropathy was considered high because subjects were previously untreated, fit and young.

Thrombocytopenia and herpes zoster infection were reported more frequently in the VcAD treatment group (50% and 16%, respectively) as compared with the VAD treatment group (39% and 3%, respectively). Hyponatremia was reported 7% vs 3% in the VcAD treatment group.

As regard the herpes zoster infection, it should be noted that, during the planned interim analysis of the study it was decided that prophylactic anti-viral therapy was to be administered for the VcAD treatment group.

Study IFM (VAD vs VcD)

478 subjects were included in the Induction Phase safety analysis set, while 207 subjects were included in the Induction Intensification Phase safety analysis set. The safety analysis set for the Transplant Phase included 406 subjects.

During induction therapy, while the overall % of adverse events, drug-related adverse events, serious adverse events, drug-related serious adverse events, Grade >3 adverse events, and drug-related Grade >3 adverse events were balanced among the VcD and VAD groups, there was a higher incidence of events of peripheral neuropathy in the VcD group compared with the VAD group (12% versus 2%, respectively).

Peripheral neuropathy with a toxicity of Grade >3 was reported in <1% of subjects in the VAD group and 5% of subjects in the VcD group. Lymphopenia, thrombocytopenia, were reported approximately 3 times more by subjects receiving VcD treatment (6%, 3%) as compared with subjects receiving VAD

treatment (2%, 1%). Further, there were less pyrexia (23 vs 13%) and nausea (29 vs 21%) in the VcD-group.

Study MMY-3010 (TD vs VcTD)

Three hundred eighty four (99%) subjects were included in the Induction Phase safety analysis set; 286 (74%) subjects were included in the Transplant Phase safety analysis set.

Overall, adverse events were experienced by 81% in the TD treatment group, 85% in the VcTD treatment group. Drug-related Grade 3 and 4 adverse events were experienced by 13% of subjects in the TD treatment group, 24% of subjects in the VcTD treatment group.

The system organ class with the highest incidence of adverse events for the TD and VcTD treatment groups was Nervous System Disorders (TD: 38%; VcTD: 60%); among this, peripheral neuropathy and peripheral sensory neuropathy (TD: 7%; VcTD: 16%) were occurring more frequently in the VcTD treatment group compared with the TD group (4%; VcTD: 34%). The incidences of Grade > 3 peripheral neuropathy events were 0% in the TD treatment group and 5% in the VcTD treatment group. The highest % of peripheral neuropathy was considered drug-related to both Velcade and Thalidomide.

Meta-analysis

Across studies, there was some variability in several categories of AE incidence, particularly serious AEs related to study drug, Grade 3 or higher AEs, and Grade 3 or higher AEs related to study drug. The rates for these categories tended to be higher in Study MMY-3003, despite fewer cycles of induction treatment administered in that study. This is most likely attributed to differences in AEs collection practices across studies.

The incidence of treatment-emergent AEs during the Induction Phase were somewhat higher for subjects in the Velcade-based induction group.

The AEs were considered drug-related for 84% and 88% of subjects in each respective treatment group. Serious treatment-emergent AEs were reported for 37% of subjects in the non-Velcade-based induction group and 41% of subjects in the Velcade-based treatment group; drug-related serious AEs were reported by 22% and 29% of subjects respectively.

Fifty-nine percent and 63% of subjects in the non-Velcade-based and Velcade-based treatment-groups, respectively, experienced at least 1 treatment-emergent AE with a toxicity Grade of 3 or higher; drug-related Grade 3 or higher treatment-emergent AEs were reported by 45% and 51% of subjects, respectively.

As compared with the non-Velcade-based group, subjects who received Velcade as an induction regimen had similar incidences in adverse drug reactions except for:

-Thrombocytopenia (non-Vc-based: 22%; Vc-based: 31%) mainly seen in Study IFM (VAD vs VcD)
-Peripheral neuropathy (non-Vc-based: 7%; Vc-based: 19%) mainly seen in Study MMY-3010 (TD vs VcTD)
-Peripheral sensory neuropathy (non-Vc-based: 7%; Vc-based: 13%) mainly seen in Study MMY-3010 (TD vs VcTD)
-Herpes zoster (non-Vc-based: 2%; Vc-based: 11%) mainly seen in Study MMY-3003 (VAD vs VcAD).

The treatment-emergent drug-related serious AEs with a toxicity Grade of 3 or higher of peripheral sensory neuropathy, peripheral neuropathy, neuralgia, and polyneuropathy were reported only by subjects in the Velcade-based group.

When comparing the TEAEs per treatment phase, it is noted that the % of grade > 3 TEAEs was higher during the transplant stage than during the induction phase although balanced between Vc-based and non-Vc-based arms; if no safety issue was associated transplant procedure (subjects not discontinued), the increase of serious AEs could be related to a treatment additive effect.

Serious adverse event / deaths / other significant events

Serious adverse events

MMY-3003: Among the most frequently reported treatment-emergent serious adverse events pulmonary embolism (VAD: 2%; and VcAD: 4%) and vomiting (VAD: 1%; and VcAD: 4%) had a higher incidence in the VcAD arm. Treatment-emergent serious adverse events of peripheral sensory neuropathy, peripheral neuropathy, and neuralgia were reported only by subjects receiving VcAD induction treatment (5%, 2%, and 3%), respectively. The overall SAE rate was high compared to studies with previously treated MM patients.

The most frequently reported treatment-emergent serious AEs are presented in the table below.

Table 15 – Treatment-Emergent serious adverse events in at least 2% of subjects in any treatment group by System Organ Class and Preferred Term during induction

(Study MMY-3003: Safety for Induction Analysis Set)

MedDRA System Organ Class Preferred Term	VAD (N=411) n (%)	VcAD (N=410) n (%)
Total no. subjects with treatment-emergent serious adverse events	166 (40)	219 (53)
Infections and infestations	69 (17)	75 (18)
Pneumonia	32 (8)	30 (7)
Herpes zoster	2 (<1)	10 (2)
Nervous system disorders	13 (3)	65 (16)
Peripheral sensory neuropathy	0	22 (5)
Neuralgia	0	14 (3)
Polyneuropathy	1 (<1)	10 (2)
Neuropathy peripheral	0	7 (2)
General disorders and administration site conditions	41 (10)	52 (13)
Pyrexia	28 (7)	29 (7)
Malaise	2 (<1)	7 (2)
Gastrointestinal disorders	29 (7)	51 (12)
Vomiting	4 (1)	16 (4)
Nausea	4 (1)	13 (3)
Diarrhoea	7 (2)	12 (3)
Constipation	4 (1)	9 (2)
Respiratory, thoracic and mediastinal disorders	23 (6)	27 (7)
Pulmonary embolism	9 (2)	16 (4)
Vascular disorders	21 (5)	26 (6)
Deep vein thrombosis	13 (3)	12 (3)
Metabolism and nutrition disorders	18 (4)	18 (4)
Dehydration	4 (1)	10 (2)
Blood and lymphatic system disorders	13 (3)	15 (4)
Febrile neutropenia	9 (2)	6 (1)

VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcAD=VELCADE, doxorubicin (Adriamycin), dexamethasone

Note: Percentages calculated with the number of subjects in each group as denominator.
Incidence is based on number of subjects, not the number of events.
Adverse Events are coded using MedDRA 13.1.

IFM: The overall SAE rate was comparable between the two treatment arms: VAD vs. VcD. All treatment-emergent serious adverse events were reported at low incidences (4% or less) as summarised in the table below.

Table 16 – Treatment-Emergent serious adverse events in at least 2% of subjects in any treatment group by System Organ Class and Preferred Term during induction

(Study IFM 2005-01: Safety for Induction Analysis Set)

MedDRA System Organ Class Preferred Term	VAD(A1+A2) (N=239) n (%)	VcD(B1+B2) (N=239) n (%)
Total no. subjects with treatment-emergent serious adverse events	82 (34)	68 (28)
Infections and infestations	30 (13)	18 (8)
Pneumonia	9 (4)	3 (1)
Pneumonia pneumococcal	5 (2)	3 (1)
General disorders and administration site conditions	17 (7)	13 (5)
Pyrexia	9 (4)	3 (1)
Respiratory, thoracic and mediastinal disorders	12 (5)	9 (4)
Pulmonary embolism	7 (3)	4 (2)
Blood and lymphatic system disorders	8 (3)	6 (3)
Neutropenia	4 (2)	0
Musculoskeletal and connective tissue disorders	8 (3)	6 (3)
Back pain	4 (2)	3 (1)

VAD=vincristine, doxorubicin (Adriamycin), dexamethasone; VcD=VELCADE, dexamethasone; A1=VAD only; A2=VAD plus DCEP; B1=VcD only; B2=VcD plus DCEP

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. Adverse Events are coded using MedDRA 13.1.

MMY-3010: Serious AEs were experienced by 33% of subjects in the TD treatment group and 26% of subjects in the VcTD treatment group and the most frequent treatment-emergent SAEs are presented in the table below. All other serious AEs occurred at a ≤2% incidence in the TD and VcTD treatment groups. Drug-related serious AEs were experienced by 10% in the TD treatment group, 10% in the VcTD treatment group, and 5% in the VBMCP-VBAD/Vc treatment group. No individual drug-related serious AE was experienced by more than 2% of subjects in any treatment group.

Table 17 – Treatment-Emergent serious adverse events during induction stage by System Organ Class and Preferred Term in >= 2% of subjects in any treatment group

(Study MMY-3010: Safety for Induction Analysis Set)

MedDRA System Organ Class Preferred Term	TD (N=126) n (%)	VcTD (N=130) n (%)	VBMCP-VBAD/Vc (N=128) n (%)
Total no. subjects with treatment-emergent serious adverse events	42 (33)	34 (26)	47 (37)
Infections and infestations	14 (11)	18 (14)	21 (16)
Pneumonia	7 (6)	9 (7)	5 (4)
Febrile infection	0	2 (2)	1 (1)
Respiratory tract infection	3 (2)	2 (2)	0
Septic shock	2 (2)	2 (2)	0
Device related infection	0	0	2 (2)
Herpes zoster	0	0	2 (2)
Respiratory, thoracic and mediastinal disorders	8 (6)	5 (4)	11 (9)
Respiratory failure	1 (1)	2 (2)	1 (1)
Dyspnoea	2 (2)	1 (1)	4 (3)
Productive cough	0	0	2 (2)
Pulmonary embolism	3 (2)	0	3 (2)
General disorders and administration site conditions	8 (6)	4 (3)	8 (6)
Pyrexia	3 (2)	4 (3)	5 (4)
Death	4 (3)	0	2 (2)
Nervous system disorders	1 (1)	4 (3)	3 (2)
Neuropathy peripheral	0	3 (2)	1 (1)
Gastrointestinal disorders	3 (2)	3 (2)	7 (5)
Intestinal obstruction	2 (2)	0	0
Vascular disorders	6 (5)	3 (2)	5 (4)
Orthostatic hypotension	0	2 (2)	0
Embolism arterial	3 (2)	1 (1)	2 (2)
Thrombosis	2 (2)	0	3 (2)
Hepatobiliary disorders	0	2 (2)	0
Hepatitis	0	2 (2)	0
Musculoskeletal and connective tissue disorders	3 (2)	2 (2)	6 (5)
Arthralgia	0	0	2 (2)
Back pain	0	0	3 (2)
Blood and lymphatic system disorders	0	1 (1)	2 (2)
Febrile neutropenia	0	1 (1)	2 (2)
Renal and urinary disorders	4 (3)	1 (1)	1 (1)
Renal failure	4 (3)	1 (1)	1 (1)
Immune system disorders	2 (2)	0	0
Amyloidosis	2 (2)	0	0

TD=thalidomide, dexamethasone; VcTD=VELCADE, thalidomide, dexamethasone; VBMCP=vincristine, carmustine (BCNU), melphalan, cyclophosphamide, prednisone; VBAD=vincristine, carmustine (BCNU), doxorubicin (Adriamycin), dexamethasone; Vc=VELCADE

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

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Adverse Events are coded using MedDRA 13.1.

Deaths

MMY-3003: 7% of subjects in both the VcAD and VAD treatment groups died during treatment. No difference in the causes or timing of death were seen between the treatment groups.

IFM: 3% of subjects in the VAD group and 1% of subjects in the VcD died during treatment. The causes of death are comparable between the two treatment groups.

MMY-3010: 5% of patients in the TD treatment group and 3% in the VcTD treatment group died during treatment. Most deaths during the Induction Phase (11 subjects) were due to adverse events.

The addition of Velcade to induction or maintenance treatment did not increase the overall incidence of death during treatment (5% non-Vc-based vs 4% Vc-based regimens).

Adverse event of interest: peripheral neuropathy

Peripheral neuropathy was the most frequently reported TEAE and the most frequent cause of discontinuation in patients treated with Vc-based therapies among the three studies.

The table below presents the incidence of peripheral neuropathy for the full duration of the induction phase for each study (VcD=4 x 21 day cycle; VcAD=3 x 28 day cycle; VcTD=6 x 28 day cycle).

Table 18 – Incidence of peripheral neuropathy during induction treatment by NCI toxicity grade and treatment discontinuation due to peripheral neuropathy: 2-Agent and 3-Agent induction regimens used in the applications studies

	MMY-3003		IFM 2005-01		MMY-3010		MMY-3006	
	VAD (N=411) %	VcAD (N=410) %	VAD (N=239) %	VcD (N=239) %	TD (N=126) %	VcTD (N=130) %	TD (n=238) %	VcTD (n=236) %
All Grade PN	27	41	3	15	12	45	14	34
≥ Grade 2	8	21	1	10	2	31	6	16
≥ Grade 3	1	7	<1	5	0	5	2	10
Induction d/c for PN	NA[a]	NA[a]	<1	2	1	5	NR	1

d/c=discontinuation; NA=not available; NCI=National Cancer Institute; NR=not reported; PN=peripheral neuropathy; TD=thalidomide, dexamethasone; VAD= vincristine, Adriamycin, dexamethasone; VcAD= VELCADE, Adriamycin, dexamethasone; VcD=VELCADE, dexamethasone; VcTD=VELCADE, thalidomide, dexamethasone

[a] Discontinuation of induction treatment in Study MMY-3003 could not be calculated due the manner in which data were recorded in the case report form.

Note: Peripheral neuropathy for Studies MMY-3003, IFM 2005-01, and MMY-3010 included the preferred terms: neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy. The specific terms comprising peripheral neuropathy in Study MMY-3006 were not defined. All Grade PN reported as "neuropathy" in Study MMY-3006.

Source: First Request for Supplemental Information response Attachment 3; Mod5.3.5.1\MMY-3003\Table41, Mod5.3.5.1\IFM2005-01\Table 29, Mod5.3.5.1\MMY-3010\Table 65; Attachment 1; Attachment 2; Attachment 3; Attachment 4, Cavo. et al[2]

The MAH also compared the incidence of peripheral neuropathy observed in studies MMY-3010 and MMY-3006 both using VcTD vs TD with the incidence observed in the VISTA study (Study MMY-3002) in which Velcade was associated to Melphalan Prednisone. In addition, a comparison with the APEX study (Study M34101-039) in which Velcade was given in monotherapy is presented in the table below.

Table 19 – Incidence of peripheral neuropathy by grade for historical Velcade registration studies

	M34100-024 M34100-025	M34101-039		MMY-3002		MMY-3021	
	Vc-treated (1.3 mg/m^2) (N=228) %	D (N=332) %	Vc (N=331) %	MP (N=337) %	VcMP (N=340) %	Vc-IV (N=74) %	Vc-SC (N=147) %
All Grade PN	37	9	37	5	47	53	38
≥ Grade 2	NR	2	27	1	32	41	24
≥ Grade 3	14	1	9	0	14	16	6

D=dexamethasone; IV=intravenous; MP=melphalan, prednisone; NR=not reported; PN=peripheral neuropathy; SC=subcutaneous; Vc=VELCADE

Source: MPI Neuropathy Report[9] Table 5; M34101-039 CSR[10] Table 14.3.1.14, Table 14.3.1.16; M34101-039 CSR update[11] Table 9-7, Table 9-8; MMY-3002 CSR[12] Attachment 3.4.2; MMY-3021 CSR[13] Table 18

Laboratory findings

MMY-3003: few (3% or less) Grade 3 abnormalities in the VAD and VcAD treatment groups and 1% or less Grade 4 abnormalities. Shifts from Grade 0 or 1 to Grade 3 or 4 in haematology analytes were reported more in the VAD treatment group compared to VcAD treatment group (30% vs. 14%). Thrombocytopenia was reported more frequently in the VcAD treatment group as compared with the VAD treatment group (50% vs 39%). No new safety concerns were observed in this study.

IFM: Subjects receiving VcD treatment had more abnormalities in haemoglobin measurements and platelet counts compared with subjects receiving VAD treatment. Lymphopenia, thrombocytopenia, were reported approximately 3 times more by subjects receiving VcD treatment (6%, 3%) as compared with subjects receiving VAD treatment (2%, 1%). Shifts from Grade 0 or 1 to Grade 3 or 4 for hemoglobin abnormalities were reported in 4% of subjects in the VAD group and 17% of subjects in the VcD group; however, this is acceptable. The low hemoglobin level is not usually a reason for dose adjustment. No new safety concerns were observed in this study.

MMY-3010: More subjects receiving VcTD had abnormalities in haemoglobin measurements and platelet counts compared with baseline. Shifts from Grade 0 or 1 to Grade 3 or 4 in haematology analytes were reported at a low frequency in all Induction Phase treatment groups. No new safety concerns were observed in this study.

Safety in special populations

No dedicated study was performed in special population.

In the meta-analysis, an evaluation of stratification factors revealed increased incidences (ie, differences >10%) in the Velcade-based induction group as compared to the non-Velcade-based induction group. These Velcade-related events are consistent with the known safety profile of Velcade of the following AES:

-Peripheral neuropathy (age: >55 years; sex: men; stage of disease: ISS Stages I and II; cytogenetic classification: standard and high risk; renal function: <60 mL/min),

-herpes zoster (stage of disease: ISS Stage III; cytogenetic classification: high risk),

-constipation (stage of disease: Stage III; renal function: <60 mL/min).

Discontinuation due to adverse events

In study **MMY-3003**, 16% (4% due to AEs) in VAD group and 14% (7% due to AEs) in VcAD discontinued after induction.

Only 229 patients from the VcAD group continued to the maintenance therapy after auto-SCT compared to 271 patients from the VAD group. Fewer subjects from the VcAD induction treatment group entered the maintenance phase, primarily due to persisting toxicity (mainly peripheral neuropathy) and ineligibility for further treatment. More subjects in VcAD induction treatment group experienced peripheral neuropathy during induction treatment (all peripheral neuropathy events: 41%, Grade ≥3: 7%) compared with the VAD induction treatment group (all peripheral neuropathy events: 27%, Grade ≥3: 1%) However, the reverse scenario was observed during the maintenance treatment phase. More subjects developed peripheral neuropathy during thalidomide maintenance treatment compared with Velcade maintenance treatment (all peripheral neuropathy events: 52%, Grade ≥3: 7% for thalidomide maintenance; all peripheral neuropathy events: 34%, Grade ≥3: 4% for Velcade maintenance)

Eighty-five (31%) of 271 subjects from the VAD induction treatment group discontinued thalidomide maintenance treatment due to adverse events (mainly peripheral neuropathy) compared with 26 (11%) of 229 subjects from the VcAD induction treatment group.

In Study **IFM 2005-01**, 5% and 8% of subjects experienced a treatment-emergent AEs leading to the discontinuation of VAD or VcD treatment, respectively; drug-related treatment-emergent AEs leading to the discontinuation of VAD or VcD treatment occurred in 3% and 5% of subjects, respectively. Most of the treatment-emergent AEs leading to the discontinuation of induction treatment occurred in the Nervous System Disorder SOC (3% in VcD vs 1% in VAD).

In Study **MMY-3010**, 6% of subjects in the TD and VcTD treatment groups experienced a treatment-emergent AEs leading to the discontinuation of induction treatment. Most of the treatment-emergent AEs leading to the discontinuation of induction treatment occurred in the Nervous System Disorder SOC (TD: 2%; VcTD: 5%).

Considering the subject disposition in the **pooled analysis**, in the post induction phase the % of discontinuation appears slightly lower in the Vc-based treatment (15% vs 20%). The picture is different when considering discontinuation in the post transplant phase; in this case, an higher % of events leading to discontinuation was observed in the Vc-based treatment (30% vs 20%) mostly due to AEs (12% Vc-based vs 3% non-Vc-based).

Dose Modifications

MMY-3003 (VAD vs VcAD): the dose of Velcade was reduced for 16% of subjects in the VcAD treatment group; in 4% of subjects the dose of Velcade was reduced due to neurotoxicity.

IFM (VAD vs VcD): the dose of Velcade was reduced for 13% of subjects receiving VcD treatment group: the most frequently cited reasons for reductions in the dose of Velcade were AEs (6%).

Treatment-emergent AEs leading to any dose modification were reported by 9% (VcD) and 2% (VAD) of subjects, with 8% (VcD) and 2% (VAD) of these AEs being drug-related. Peripheral neuropathy was the most frequently reported treatment-emergent AE leading to a dose modification.

MMY-3010 (TD vs VcTD): the dose of Velcade was reduced for 31% of subjects in the VcTD treatment group. Treatment-emergent AEs leading to any dose modification were reported by 35% (VcTD), 7% (TD); most of these AEs were drug-related (34%, 6%) respectively. Peripheral neuropathy was the most frequently reported treatment-emergent AEs leading to a dose reduction (TD: 5%; VcTD: 27%).

2.5.1. Discussion on clinical safety

Although no unexpected adverse drug reactions were reported in patients treated with Velcade, when considering the pooled analysis across the three studies, the events for which the incidence is most different between subjects who received Vc-based treatment and non-Vc-treatment were thrombocytopenia, peripheral neuropathy, peripheral sensory neuropathy, and Herpes zoster.

Among the 3 studies, Study MMY-3003 (VAD vs VcAD) was the one with the highest % of serious TEAEs: This % was higher in the VcAD mostly due to higher rate of nervous system disorders (peripheral sensory neuropathy, peripheral neuropathy, and neuralgia) and infections (herpes zoster, pneumonia) compared to the VAD arm. Particularly, this combination regimen showed a numerically higher rate of Grade ≥2 (21%) and Grade ≥3 (7%) peripheral neuropathy compared with double-

agent VcD regimen (10% and 5%). The high incidence of herpes zoster infection in VcAD arm was reported although the administration of a prophylactic anti-viral therapy. Of note, this was the study in which the less number of Velcade treatment cycles was used (3 cycles; 4 cycles in study IFM and 6 cycles in study MMY-3010). This study also reported the highest % of discontinuation after induction (16% VAD vs 14% VcAD); although the % was almost similar, in the VcAD arm a higher % (7%) of subjects discontinuation was due to AEs (vs 4% VAD). Velcade dose reduction was needed in 16% of patients mostly due to neurotoxicity. Further to these concerns, this combination VcAD was not considered approvable.

In study IFM (VAD vs VcD), the % of serious TEAEs was slightly lower in the VcD (28% vs VAD 34%); it should be noted that in this study Velcade was combined only to dexamethasone instead of two chemotherapics. Thrombocytopenia was reported approximately 3 times more by subjects receiving VcD treatment (3%) as compared with subjects receiving VAD treatment (1%). However, in this study 8% in VcD arm vs 5% in VAD arm discontinued during the induction phase mostly due to Nervous System Disorders. Velcade dose reduction was needed in 13% of patients mostly due to neurotoxicity.

Among the three studies, Study MMY-3010 (TD vs VcTD) was the one with the highest % of Velcade dose reduction (31%); however, that did not affect the discontinuation that happened in 6% of subjects in both arms. Peripheral neuropathy was the most frequent cause of discontinuation as well as the most frequently reported TEAEs (TD: 7%; VcTD: 16%) with the highest % among the three studies.

The neurotoxicity of bortezomib is a known adverse drug reaction of this drug in the treatment of patients with MM. Peripheral neuropathy was the most frequently reported TEAE and the most frequent cause of discontinuation in patients treated with Vc-based therapies among the three studies. It is acknowledged that a similar and consistent incidence of all grade and >3 grade peripheral neuropathy across the three studies was shown. However, this comparison among trials using different combined regimens and different treatment cycles has intrinsic limitations that reduce the strength of the evidence.

The incidence of Grade ≥2 peripheral neuropathy for the double-agent VcD induction regimen, as investigated in Study IFM 2005-01 (10%) was numerically lower than the corresponding rates of Grade ≥2 peripheral neuropathy reported for the triple-agent VcAD and VcTD treatment groups from Studies MMY-3003 and MMY-3010 (21% and 31%, respectively). The rate of Grade ≥2 peripheral neuropathy for the VcD regimen (10%) was also numerically lower than that observed for Grade ≥2 peripheral neuropathy for the VcTD regimen in Study MMY-3006 (16%), although the difference was less pronounced. The VcD regimen from Study IFM 2005-01 and VcTD regimen from Study MMY-3010 shared an identical rate of Grade ≥3 peripheral neuropathy (5%), which was similar to the rate observed for the VcAD regimen from Study MMY-3003 (7%) and numerically lower than was reported for the VcTD regimen from Study MMY-3006 (10%).

The rates of peripheral neuropathy events observed for the VcTD treatment group were similar in studies MMY-3006 and MMY-3010 despite the difference in number of induction cycles in the studies (3 cycles MMY-3006 vs 6 cycles in MMY-3010).

Comparison of results (both efficacy and safety) from different studies sharing common arms, should be considered with caution even if the population enrolled apparently look homogeneous. However, data on grade 2 neurotoxicity from different studies with Vc are considered useful as a possible reference of neurotoxicity incidence generally observed with Vc administered either alone or in combination. From the submitted data, Vc single agent-induced grade >2 neurotoxicity ranged from 24% (SC) to 41% (IV) in second line, whereas the combination of Vc with melphalan and prednisone

(VcMP) was associated with 32% grade >2 neurotoxicity in the front line setting of the VISTA study (MMY-3002). These incidences were considered acceptable and balanced versus efficacy outcomes when the SC route was registered (X/47) and when the front line setting was approved (II/28).

Also in the studies submitted in this application, grade >2 neurotoxicity is highly variable being 10% (VcD), 21% (VcAD) and 31% (VcTD): even in the same treatment arm VcTD the incidence is highly variable (16% in supportive study MMY-3006 and 31% in MMY-3010).

The incidence of discontinuation for peripheral neuropathy and grade >3 neurotoxicity is overall similar among the studies; discontinuation was slightly higher in study MMY-3010 VcTD (5%) and grade >3 neurotoxicity was slightly higher in the supportive study MMY-3006 (10%) in which the incidence of grade > 2 neurotoxicity was lower. The lower incidence of Grade >3 neurotoxicity demonstrates that Grade >2 neurotoxicity was well manageable.

Therefore, a warning has been included on the need for early and regular monitoring for symptoms of treatment emergent neuropathy with neurological evaluation in patients receiving Velcade in combination with medicinal products known to be associated with neuropathy (e.g. thalidomide) and that appropriate dose reduction or treatment discontinuation should be considered (see section 4.4 of the SmPC). Furthermore, the posology recommendations for the VcTD combination should be of four 28-day cycles, followed by 2 additional cycles in patients with at least partial responses (see section 4.2 of the SmPC).

There was one ascertained case of “colon cancer” toxicity grade 3 reported in the VcTD arm of study MMY-3010; no other cases were found following a cumulative search in the Velcade Global Safety Database through 8 May 2013. In view of its combination with thalidomide and the concerns on the second primary malignancies (SPM, identified risk of thalidomide), the risk management plan of Velcade has been updated to include SPM as Missing Information and to use a follow-up questionnaire to collect information on any newly reported case of SPM as part of routine pharmacovigilance activities.

In addition, in view of the teratogenicity of thalidomide, the product information of Velcade has been updated to refer prescribers and patients to the thalidomide product information in order to ensure that patients receiving Velcade in combination with thalidomide should adhere to the pregnancy prevention programme of Thalidomide Celgene.

2.5.2. Conclusions on clinical safety

The VcAD combination regimen raised concerns with regards to peripheral neuropathy and herpes zoster infection. Furthermore, although no notable cardiac signals were observed in study MMY-3003, in view of the known cardiotoxicity of doxorubicin, the use of such combination as first line induction therapy may limit or prevent the possibility to use in second line therapy other agents with a known cardiotoxicity potential (e.g. Caelyx-doxorubicin pegylated liposomal, endoxan). Therefore, despite its efficacy results, this combination was not considered approvable.

The safety profile of Velcade in combination with dexamethasone or with dexamethasone and thalidomide was considered acceptable. The neurotoxicity of bortezomib is a known adverse drug reaction of Velcade in the treatment of patients with MM. Peripheral neuropathy was the most frequently reported TEAE and the most frequent cause of discontinuation in patients treated with Vc-based therapies among the three studies. However, this can be managed through posology recommendations as proposed in the SmPC.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure which included a risk minimisation plan.

Table 20 – Summary of the risk management plan

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 should be closely monitored. SmPC: Labelled in Section 4.8 Undesirable Effects.	None
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	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that treatment with	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
(including paralysis)	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 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 Effects, identifies pulmonary hypertension as a serious adverse reaction uncommonly reported during treatment with Velcade.	None
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,	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	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.	
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 abnormalities	The SmPC, Section 4.4 Special 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.	None
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	Proposed actions/components and rationale include: The company will ensure proper training of all Company

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	(Velcade with dexamethasone and with dexamethasone and thalidomide) and for additional information concerning ADRs.	representatives and MSLs on the different Velcade treatment schedules approved for transplant induction. Representatives 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/promotional 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 Transplant settings is addressed.
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 to refer to the SmPC for those products.	None

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

In addition, the CHMP noted that a consolidated version of the RMP, currently also under review in parallel as part of another extension indication application (II/63G) will be assessed by the PRAC.

2.7. Update of the Product information

The CHMP finally agreed to the following indication to be added in section 4.1 of the SmPC:

Velcade in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

As a consequence of this new indication, section 4.1, 4.2, 4.3, 4.4, 4.6, 4.8 and 5.1 of the SmPC. Particularly, a new warning with regard to reference to pregnancy testing and prevention requirements of thalidomide and a warning for early and regular monitoring for symptoms of treatment emergent neuropathy with neurological evaluation have been added to the product information. The Package Leaflet has been updated accordingly.

No full user consultation with target patient groups on the package leaflet has been performed for this extension of indication on the basis of a bridging report making reference to the current product information of Velcade. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Results from the three submitted pivotal studies showed a clear statistically and clinically significant difference in favour of Vc-based combinations in terms of complete response both in post-induction and post-transplant setting. The importance of obtaining a CR during high-dose therapy and stem cell transplantation and the association between CR and log-term outcome has been described in a number of studies and meta-analyses.

Median overall survival was not reached in any of the individual studies submitted; however, a trend favoring Velcade-based treatment was observed in each study included into the integrated analysis.

Stem cell collection was well feasible after induction treatment with Velcade-based regimen. This is of importance, as this is not the case with all currently used induction treatments.

The meta-analysis did not allow to draw any conclusion on which was the best combination treatment among the different regimens.

Uncertainty in the knowledge about the beneficial effects

Not applicable.

Risks

Unfavourable effects

The neurotoxicity of bortezomib is a known adverse drug reaction of this drug in the treatment of patients with MM. Peripheral neuropathy was the most frequently reported TEAE and the most frequent cause of discontinuation in patients treated with Vc-based therapies among the three studies.

Serious TEAEs were reported the most frequently in the VcAD combination, particularly with respect to nervous system disorders (peripheral sensory neuropathy, peripheral neuropathy, and neuralgia) and infections (herpes zoster, pneumonia), although treatment with Velcade was only received for 3 cycles in this study. The high incidence of herpes zoster infection in VcAD arm was reported although the

administration of a prophylactic anti-viral therapy. This study also reported the highest % of discontinuation after induction although balanced among arms and in the VcAD arm a higher % of subjects discontinued due to AEs. Velcade dose reduction was needed in 16% of patients mostly due to neurotoxicity.

Velcade neurotoxicity seems to be enhanced in the combination with Thalidomide, a known neurotoxic agent. The incidence of Grade ≥2 peripheral neuropathy for triple-regimen VcTD treatment was 31% vs 2% in TD arm. Thalidomide neurotoxicity is not always reversible thus it is preferably to reduce the dose of the agent that induce a less manageable toxicity. Indeed, in the VcTD arm the % of patients with 1 or 2 Thalidomide dose reductions (44% vs 32% TD) was higher than the % of patients with 1 or 2 Velcade dose reductions (31%).

Furhermore, changes in the Velcade product information have been proposed to warn on the risk of teratogenicity due to the combination with thalidomide.

Although study MMY-3006 is considered supportive, it indicates that 4 induction cycles are sufficient to achieve a good response. In study MMY-3010 the greatest toxicity was observed in cycles 5 and 6 while no major difference in efficacy was seen when comparing 6 cycles with 4 cycles. Four treatment 28-day cycles are therefore recommended and can be extended to 6 in patients with at least PR (see SmPC section 4.2).

In view of the teratogenicity of thalidomide, the product information of Velcade has been updated to refer prescribers and patients to the thalidomide product information in order to ensure that patients receiving Velcade in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide.

Furthermore, the risk management plan of Velcade has been updated to include routine pharmacovigilance activities to monitor the risk of SPM as missing Information in view of its combination with thalidomide.

Uncertainty in the knowledge about the unfavourable effects

Although comparison of results from different studies should be considered with caution, data on grade 2 neurotoxicity from different studies with Vc were considered useful as a possible reference of neurotoxicity incidence generally observed with Vc administered either alone or in combination. In the studies submitted in the present application, grade >2 neurotoxicity was highly variable being 10% (VcD), 21% (VcAD) and 31% (VcTD); of note the incidence of grade >2 neurotoxicity reported with the VcTD treatment arm were highly variable across studies (16% in supportive study MMY-3006 and 31% in MMY-3010). Consequently, a warning has been included on the need for early and regular monitoring for symptoms of treatment emergent neuropathy with neurological evaluation in patients receiving Velcade in combination with medicinal products known to be associated with neuropathy (e.g. thalidomide) and that appropriate dose reduction or treatment discontinuation should be considered (see section 4.4 of the SmPC).

Based on the evidence of a low risk of SPM (1 ascertained case of “colon cancer” toxicity grade 3 was found in VcTD arm of study MMY-3010; no other cases were found following a cumulative search in the Velcade Global Safety Database through 8 May 2013), the risk management plan of Velcade has been updated to include routine pharmacovigilance activities to monitor the risk of SPM as missing Information.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The availability of new medicinal products in the first line treatment of MM in patients suitable for HDT with auto-SCT is considered of great clinical value. The benefit of Vc-based treatments in the proposed indication was considered sufficiently proven for CR/nCR. Both the post-induction response rates as well as the post-transplant response rates in patients treated with Vc-based combination therapies are higher compared to non Vc-based regimens.

The neurotoxicity of bortezomib is a known adverse drug reaction of this drug in the treatment of patients with MM. Peripheral neuropathy was the most frequently reported TEAE and the most frequent cause of discontinuation in patients treated with Vc-based therapies among the three studies.

Benefit-risk balance

Clear evidence of efficacy of Vc-based combinations in the sought indication was provided by the submitted trials.

However, in view of the higher incidence of haematological toxicity, including thrombocytopenia, and consequent herpes zoster infections, as well as neurotoxicity ofthe combination of Velcade with doxorubicin and dexamethasone was not considered approvable.

A higher neurotoxicity incidence was associated to the greater thalidomide exposure (study MMY-3010) in terms of daily dose and treatment duration. However, this can be managed through monitoring and posology recommendations including dose reductions.

Discussion on the Benefit-Risk Balance

The efficacy in terms of response rate of the combination of Velcade with dexamethasone and doxorubicin did not outweigh its risks.

Based on the reviewed, efficacy and safety data, the benefit-risk balance of the combination of Velcade with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation was considered positive.

4. Recommendations

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

Variation accepted		**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

Extension of the indication of Velcade in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation.
Consequently, sections 4.1, 4.2, 4.3, 4.4, 4.6, 4.8 and 5.1 of the Summary of Product Characteristics

and the package leaflet have been updated. The MAH also took the opportunity to make editorial changes to the product information.