21 June 2012

EMA/432973/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VELCADE

bortezomib

Procedure No.: EMEA/H/C/000539/X/0047

Note

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

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Table of contents

List of abbreviations

ANC	absolute neutrophil count
AUC	area under the plasma concentration-time curve
AUE	area under the effect-time curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed plasma concentration
CR	complete response
CVC	central venous catheter
EBMT	European Group for Blood and Marrow Transplantation
E_{max}	observed maximum effect
EU	European Union
FDA	US Food and Drug Administration
IgA	immunoglobulin A
ISS	international staging system
ITT	intent-to-treat
IV	intravenous
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development
KPS	Karnofsky performance status
MedDRA	Medical Dictionary for Regulatory Activities
M-protein	monoclonal protein
MR	minimal/minor response
NEC	not elsewhere classified
NC	no change
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nCR	near complete response
NR	no response
ORR	overall response rate
PD	progressive disease
PFS	progression-free survival
PR	partial response
PSUR	Periodic Safety Update Report
SC	subcutaneous
SmPC	Summary of Product Characteristics
SOC	System Organ Class
T_{max}	for pharmacokinetic analysis: time when C_{max} is observed; taken directly from the plasma concentration-time profile for pharmacodynamic analysis: time when E_{max} is first observed; taken directly from the inhibition-time profile
TTP	time to disease progression
VGPR	very good partial response
vs.	versus
WBC	white blood cell

1. Scientific discussion

1.1. Introduction

Velcade (bortezomib) is a proteasome inhibitor 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. By inhibiting a single molecular target, the proteasome, VELCADE affects multiple signalling pathways. Thus, 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 was granted a marketing authorisation in the EU on 26 April 2004 and is currently indicated as follows:

VELCADE as monotherapy is indicated for the treatment of 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 patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.

Multiple myeloma (MM) is a progressive 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 (free monoclonal κ and λ light chains).

The estimated incidence of MM in Europe is 23,000 per year. MM is still considered to be an incurable disease and the 5-year relative survival rate is around 33%. Median age at diagnosis is 65 to 70 years, with the incidence of myeloma increasing with age. MM usually manifests as 1 or more lytic bone lesions, monoclonal protein in the blood or urine, and disease in the bone marrow. Disease progression is often associated with worsening of symptoms and organ dysfunction characteristic of myeloma, such as anemia, bone lesion-related symptoms, renal function impairment, and susceptibility to infections.

Current treatment options, therefore, aim not only to improve survival but also to induce tumour response, inhibit tumour progression, and delay disease-related complications.

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

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

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

Velcade is available as 1 mg and 3.5 mg powder for solution for injection to be reconstituted at 1 mg/ml for intravenous use.

If an alternative route of administration could be utilized without reduction in treatment efficacy and without the introduction of significant offsetting complications, physicians could gain additional flexibility when individualizing their patients' treatment. While non-clinical studies showed the oral route of VELCADE administration to be limited by poor bioavailability, the subcutaneous (SC) route was found to be an alternative to intravenous (IV) administration. For some patients, such as elderly or obese patients, where limited or difficult venous access or the need to preserve venous reserves present significant treatment challenges, as well as for patients who may receive prolonged treatment, SC administration was identified as a potentially useful means by which to facilitate care.

The MAH proposed in this extension application, a new subcutaneous route of administration only for Velcade 3.5 mg powder for solution for injection, to be reconstituted at 2.5 mg/ml. No changes were proposed to the VELCADE dose or treatment schedule.

1.2. Quality aspects

1.2.1. Introduction

The approved commercial dosage forms for Velcade are 1.0 mg powder for solution for injection and 3.5 mg powder for solution for injection. The subject of this line extension is the addition of the subcutaneous (SC) route of administration only for Velcade 3.5 mg presentation.

Velcade 3.5 mg powder for solution for injection for subcutaneous use is the same as that currently marketed for IV administration, the only difference being the volume and concentration of the reconstituted solution. The final concentration of the reconstituted Velcade 3.5 mg powder for solution for injection for subcutaneous use is 2.5 mg/ml.

1.2.2. Active Substance

The active substance used in the new route of administration is the same as that used in the manufacture of the already approved presentations of Velcade. There were no changes made to active substance and therefore no additional data was submitted.

1.2.3. Finished Medicinal Product

Pharmaceutical Development

The finished product is a sterile, lyophilized formulation contained in a single-use vial, each vial containing 3.5 mg of bortezomib (as the boronic acid).

The quantitative composition is the following: bortezomib as the boronic acid, 3.5 mg (active substance); mannitol 35 mg (bulking agent); t-butyl alcohol (co-solvent, eliminated during lyophilisation process); water for injection (solvent, eliminated during lyophilisation process); nitrogen

(inert gas to filter and control/break the vacuum after lyophilisation). Therefore, the final lyophilised powder of Velcade drug product contains bortezomib 3.5 mg as boronic acid and mannitol 35 mg.

When reconstituted with 3.5 ml 0.9 % Sodium Chloride for Injection for IV use, each ml contains 1 mg bortezomib and 10 mg mannitol (final concentration 1.0 mg/ml). When reconstituted with 1.4 mL 0.9 % Sodium Chloride for Injection for SC use, each ml contains 2.5 mg bortezomib and 25 mg mannitol (final concentration 2.5 mg/ml).

The finished product is contained in a 10 ml, 13 mm, USP/EP Type 1 borosilicate glass vial. The closure is a 13 mm grey lyophilization stopper, composed of a bromobutyl elastomer with inert mineral reinforcement. The drug product is sealed with a 13 mm royal blue flip-off seal.

Manufacture of the product

The manufacture of Velcade finished medicinal product starts with the formulation of the bulk solution, obtained by mixing first water for injection and t-butyl alcohol, then mannitol and the active substance are added to the formulation vessel in two consecutive steps. The bulk solution is then filtered aseptically. The filtrated solution is aseptically filled in vials, and the vials undergo the lyophilisation process. Capping, decontamination, ink-jetting, 100% visual inspection, and transfer of the vials to the labelling and packaging site for secondary packaging are the final steps of the manufacturing of Velcade finished product.

Critical manufacturing parameters have been identified and are controlled by the tests for bulk solution appearance, assay, density, bioburden, filter integrity, and fill weight checks. The overall manufacturing process is considered a non-standard process (aseptic filtration connected to lyophilisation).

Product specification

The same specifications for the reconstituted Velcade vials apply to both IV (1.0 mg/ml) and SC dosing (2.5 mg/ml). Analytical procedures for testing the reconstituted vials are the same for both IV and SC solutions except for the reconstitution volume.

Stability of the product

Compatibility and in-use stability data has been submitted for Velcade 3.5 mg powder for solution for injection for subcutaneous use to support a maximum storage time of 8 hours at 25°C for the reconstituted finished product in both vials and syringes.

The compatibility/stability studies of the 2.5 mg/ml reconstituted solution for SC use were performed using different types of commercially available syringes and in vials under the normal conditions of use. In particular, reconstituted finished product (2.5 mg/ml) was loaded in commercially available syringes from three different vendors and held for up to 24 hours at room temperature in ambient light. The following parameters were tested for the reconstituted solution held in the syringes: color and clarity of solution, particulates (visual inspection), pH, assay, and impurities. The results were compared to a baseline control solution in the original product vial. In addition, the appearance of the unreconstituted finished product and of the reconstituted solution were also evaluated for 24h at both 5°C (protected from light) and room temperature (ambient light). The results were well within the

specifications and show a good consistency with the 1.0 mg/ml reconstituted solution as well as with the baseline control.

Furthermore, the stability of three batches of 2.5mg/ml reconstituted solution in vials has been tested for up to 24h at both 5°C and room temperature. The results were well within the specifications.

The compatibility of Velcade with the recommended reconstitution diluent, 0.9%w/v sodium chloride solution for injection have been demonstrated in reconstitution stability studies, and compatibility with common dosage administration devices has also been demonstrated.

Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are accepted.

1.2.4. Discussion on chemical, pharmaceutical and biological aspects

Velcade 3.5 mg powder for solution for infusion for SC use is the same as that currently marketed for IV administration, the only difference being the final volume and concentration of the reconstituted solution (1.4 ml, 2.5 mg/ml for SC use vs. 3.5 ml, 1.0 mg/ml for IV use).

Compatibility and stability results for the 2.5 mg/ml reconstituted solution in syringes and vials were well within the specification, supporting the proposed in-use shelf life of 8 hours at 25oC, as currently approved for the 1.0 mg/ml reconstituted solution.

1.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

1.3. Non-clinical aspects

1.3.1. Introduction

Non-clinical studies TOX-7345, TOX-8394 were conducted in accordance with GLP. Non-clinical studies RPT-00526, RPT-00537, KLA-00236, TOX-6863, "Mouse Multiple Myeloma Model" were not conducted in accordance with GLP. Study reports were written according to internal standard operative procedures.

1.3.2. Pharmacology and pharmacokinetics

The pharmacodynamic (PD) of bortezomib after IV administration has been previously studied and described at the time of granting marketing authorisation.

In the present application, the pharmacokinetics (PK) and PD of bortezomib were evaluated after SC, IV, and PO administration in single and repeat-dose multi-cycle toxicity studies in cynomolgus

monkeys by measuring blood 20S proteasome inhibition (Studies RPT-00526, RPT-00537). In addition, the anti-tumour effect of SC administered bortezomib was evaluated in the 5T2MM mouse model.

Pharmacodynamic Effects on a Mouse Multiple Myeloma Model

The effect of bortezomib administered SC on tumour burden and MM-related bone disease in a repeat-dose study in the 5T2MM murine model of myeloma (Deleu S et al. Cancer Res 2009, 69 (13): 5307-5311).

In a 5T2MM mouse model, SC administration of bortezomib at 0.6 mg/kg (1.8 mg/m^2) or 0.8 mg/kg (2.4 mg/m^2), BIW, significantly decreased the burden of MM by significantly decreasing the number of plasma cells and serum paraprotein levels, decreasing angiogenesis and MM bone disease.

RPT-00526 –Pharmacokinetics and Pharmacodynamics study of Bortezomib after Oral, Intravenous and Subcutaneous Administration of Bortezomib to Male Cynomolgus Monkeys

Male Cynomolgus monkeys (4/group) were administered bortezomib twice weekly for two weeks (Days 1, 4, 8, and 11) by IV, PO, or SC administration at doses of 0.1, 0.3, and 0.1 mg/kg, respectively. Serial blood samples were collected into tubes containing tri-potassium ethylenediaminetetraacetic acid (K3EDTA) from all animals after each dose. Plasma and red blood cells were prepared from the blood samples. Bortezomib concentrations were quantified in the plasma using a liquid chromatography with a tandem mass spectrometry (LC/MS/MS)-based method. Levels of inhibition of 20S proteasome activity were determined using an ex vivo spectrofluorometric assay in whole blood and red blood cells. In addition, bortezomib concentrations were determined in whole blood and red blood cells but the data is not presented in this report due to analytical issues.

Bortezomib was detected in plasma through 48 hours post IV administration for all 4 doses. After PO administration bortezomib could be detected through 4, 8, 24, and 48 hours post-dose for doses 1, 2, 3, and 4, respectively. After SC administration, bortezomib was detected in the plasma through 48 hours post-dose after Dose 1 and Dose 4, and through 24 hours post-dose after Dose 2 and Dose 3.

VELCADE was administered by IV bolus (0.1 mg bortezomib/kg), oral gavage (0.3 mg bortezomib/kg), or SC (0.1 mg bortezomib/kg) to four animals/group on Days 1, 4, 8, and 11, and samples for PK (plasma, whole blood, and red blood cells) and PD (whole blood and red blood cells) analysis were collected after each dose.

The absorption of bortezomib was rapid after SC administrations.

After Dose 1, the time at which the maximum concentrations of bortezomib after IV, PO, and SC administration occurred (Tmax) were 0.3, 1.0, and 0.3 hours post-dose, respectively. After Dose 4, the Tmax occurred at 0.3, 0.8, and 0.4 hours post-dose, respectively.

After Dose 1, the mean observed peak plasma concentrations (Cmax) after IV, PO, and SC administration were 23.5, 6.73, and 49.5 ng/mL, respectively. After dose 4, the Cmax concentrations were 28.2, 6.27, and 51.7 ng/mL, respectively.

After Dose 1, the mean area under the plasma concentration versus time curve (AUC0-72hr) values after IV, PO, and SC administration were 35.5, 15.1, and 64.2, hours*ng/mL, respectively. After Dose 4, the AUC0-72hr values were 76.6, 23.8, and 107, hours*ng/mL, respectively.

The rank order of exposure to bortezomib in the plasma, as measured by Cmax and AUC, was SC administration, IV administration, and oral administration. The reason for the higher exposure after SC administration compared to IV administration at the same dose is unknown.

Comparable to IV, for the SC administration the level of proteasome inhibition increased sharply over a small concentration range before reaching a plateau.

Oral administration resulted in a greater variability and a weak correlation between plasma concentrations of bortezomib and proteasome inhibition.

RPT-00537 –Pharmacokinetics and pharmacodynamics study of Bortezomib after Intravenous or Subcutaneous Administration of Bortezomib to Male Cynomolgus Monkeys

Male cynomolgus monkeys (4/group) were administered a single dose of bortezomib by IV or SC administration at a dose of 0.1 mg/kg. Following administration serial samples for PK (plasma) and PD (whole blood) analysis were collected from all animals. Bortezomib concentrations were quantified in the plasma using a liquid chromatography with a tandem mass spectrometry (LC/MS/MS)-based method.

Levels of inhibition of 20S proteasome activity were measured using an ex vivo spectrofluorometric assay in whole blood.

Bortezomib was detected in plasma through 72 hours post-dose after IV and SC administration. The time at which the maximum plasma concentrations of bortezomib after IV and SC administration occurred (Tmax) were 0.1 and 0.4 hours post-dose, respectively.

The mean observed peak plasma concentrations (Cmax) were 57.4 and 35.2 ng/mL, respectively. The mean area under the plasma concentration versus time curve (AUC 0-72hr) values were 53.1 and 85.9 hr*ng/mL, respectively.

Exposures to bortezomib in the plasma were broadly similar between SC and IV administration with exposure as measured by Cmax being slightly higher after IV administration and exposure as measured by AUC being higher after SC administration.

The reason the AUC after subcutaneous administration is higher than the AUC after IV administration is unknown.

Administration of bortezomib by IV and SC administrations reached similar levels of inhibition of 20S proteasome activity with a delay in maximal inhibition from SC administration when compared to IV administration. The mean maximum levels of 20S proteasome inhibition after IV and SC administration were 80.4% and 78.7%, respectively.

Proteasome inhibition was maximal at 0.25-0.5 hours post-dose after IV administration and 1 hour post-dose after SC administration.

With IV administration where the level of proteasome inhibition increased sharply over a small concentration range and reaching a plateau. Proteasome inhibition after SC administration increased more gradually over a broader range of bortezomib concentrations.

1.3.3. Toxicology

Table 1 – Overview of toxicology studies

ReportNumber /GLP status	Species/Strain/Sex	Dosing Regimen	Route of administration	Dose (mg/kg [mg/m²])
KLA00236[1] (non-GLP)	Monkey/cynomolgus/ Male Group 1: 1M Group 2: 3 M	Dosing on Days 1, 8 and 15, followed by 10-day recovery (=dose-free holiday)	SC	Group 1: Day 1: 0.166 [2.0]; Day 8&15: 0.182 [2.2] Group 2: 0.166 [2.0]
TOX7345[2] (GLP)	Monkey/cynomolgus/ Male/female 3/sex/group	4 cycles[a]	SC	0.075 [0.9] 0.1 [1.2]
		QW for 12 weeks 4 cycles[a]	SC IV	0.166 [2.0] 0.1 [1.2]
TOX8394[3] (GLP)	Monkey/cynomolgus/ Male/female 3/sex/group	5 consecutive days for 8 weeks[b]	SC	0.0166 [0.2] 0.0333 [0.4] 0.05 [0.6]
TOX6863[4] (Local Tolerance; non-GLP)	Rabbit/NZW/ Female 3/group	Single dose	SC at 1.0 or 3.5 mg/mL	0.1 [1.2]

[a] Dosing on Days 1, 4, 8 and 11, followed by 1 week of recovery (=dose-free holiday) = 1 cycle, for 4 cycles (12 weeks).
[b] Dosing once daily for 5 consecutive days, followed by a 2-day recovery period (=dose-free holiday), for a total of 8 weeks.
GLP= Good Laboratory Practice; IV = intravenous(ly); NZW = New Zealand white; QW = once weekly; SC = subcutaneous(ly)

Repeat dose toxicity

The toxicity of bortezomib after SC administration was characterised in repeat-dose toxicity studies in Cynomolgus monkeys and was compared with the known toxicological profile of bortezomib administered IV. Information on local tolerability and tissue reaction after SC administration of bortezomib was obtained from a single-dose study in rabbits.

KLA-00236 – 3-week Repeat Dose Toxicity Study in Cynomolgus Monkey

This was a preliminary toxicology study. The objective of this study was to determine the potential systemic toxicity of VELCADE when administered SC in male Cynomolgus monkeys and to determine the persistence or reversibility of any finding after a 10-day recovery period.

The study consisted of two groups of male Cynomolgus monkeys receiving either an escalating dose regimen of VELCADE (0.166 mg/kg [2.0 mg/m²] on Day 1, and 0.182 mg/kg [2.2 mg/m²] on Days 8 and 15; Group 1 – 1 animal) or VELCADE (0.166 mg/kg [2.0 mg/m²] for three weekly doses; Group 2 – 3 animals) by SC injection. Effects of VELCADE were monitored by clinical observations, body weights, and periodic assessment of haematology parameters. After the final blood sample collection time point on Day 26, all surviving animals were released to the Test Facility.

The Group 1 animal that was dosed at 0.166 mg/kg for the first dose and then 0.182 mg/kg at the second and third doses did not exhibit clinical signs; however, all the animals had notably elevated white blood cell parameters during the dosing period. The apparently normal values at Day 26 indicate that the alterations were reversible.

Dosing with VELCADE at 0.166 mg/kg once weekly for 3 weeks resulted in a number of clinical signs for the two Group 2 animals that survived. For one of these animals, the clinical signs resolved, but for the other there was still skin erythema and dry flaky skin at the end of the 10-day recovery period.

The one Group 2 animal that was euthanized after the first dose at 0.166 mg/kg had a gastric ulcer that may have been pre-existing and exacerbated by the dosing.

TOX7345 – 12-week (4 cycles) Repeat dose Toxicity Study in Cynomolgus Monkey

This study was to investigate the potential subchronic toxicity of bortezomib in the cynomolgus monkey following up to 4 cycles of 11 days of administration by subcutaneous and intravenous injection. Each of cycles 1, 2 and 3 consisted of dosing on Days 1, 4, 8 and 11, followed by 1 week of recovery and cycle 4 consisted of dosing on Days 1, 4, 8 and 11 with terminal euthanasia 72 hours later. In addition, the toxicity of bortezomib was investigated when administered once weekly by subcutaneous injection to cynomolgus monkeys for up to 12 weeks. Furthermore, the PK/PD of bortezomib was evaluated after chronic dosing by subcutaneous versus intravenous routes.

The study design is detailed in the table below.

Table 2 – Study TOX7345 design

Group No Identification	Dose Level (mg/kg/dose)	Dose Level (mg/m^2/dose)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Main Study No. of Animals Males	Females
1. Control SC [a]	0	0	0.0474	0	3	3
2. Low-dose SC [a]	0.075	0.9	0.0214	3.5	3	3
3. Mid-dose SC [a]	0.1	1.2	0.0285	3.5	3	3
4. High-dose SC [b]	0.166	2.0	0.0474	3.5	3	3
5. High-dose IV [a]	0.1	1.2	0.1	1.0	3	3

[a] Dosing for 4 cycles (Cycles 1, 2 and 3 =dosing on Days 1, 4, 8 and 11, followed by 1 week of recovery: Cycle 4 = dosing on Days 1, 4, 8 and 11 with terminal euthanasia 72 hours after the last dose)
[b] Once weekly dosing for 12 weeks with terminal euthanasia 72 hours after the last dose.

The following were evaluated: clinical signs and food consumptions (daily), injection sites (pre-dose on each dosing day), body weight (weekly), neurological parameters, ophthalmology (pre-treatment and Week 10/11) and electrocardiograms (pre-treatment and Day 72). In addition, samples were collected for haematology and serum biochemistry (pre-treatment and Days 14, 35 and 77 for Groups 1, 2, 3 and 5; pre-treatment and Days 11, 32, 53 and 81 for Group 4), urinalysis (Days 14, 21, 35, 42, 63 and 77 for Groups 1, 2, 3 and 5; Days 11, 14, 32, 35, 53, 56,77 and 81 for Group 4), toxicokinetics and pharmacokinetics (Days 1, 32, and 7 for Groups 1, 2, 3 and 5; Days 1, 50 and 78 for Group 4). At the end of the treatment period, macroscopic observations were collected at necropsy, selected organs were weighted and protocol directed tissues were microscopically examined.

Main toxicity included chronic emesis and diarrhoea, body weight loss, alterations in serum biochemistry parameters and microscopic lesions in peripheral nervous system and spinal cord, renal cortical tubular degeneration/hypertrophy, hypocellularity in bone marrow, and atrophy of lymph nodes.

The adverse event profile of VELCADE at dose level of 1.66mg/Kg/dose QW for 12 weeks was similar although more pronounced when compared to that observed following SC or IV administration at 0.1 mg/kg.

The no-adverse-effect-level was not determined in this study. The MTD was reached at 0.1mg/kg for both SC and IV administrations (4 cycles of twice weekly dosing followed by one week untreated), but could not be determined for the weekly injection. Minor histopathological changes were observed in peripheral nervous system (numerically higher following SC administration) and spinal cord, lymph nodes and kidneys following MTD of VELCADE.

Comparison of the plasma exposure of bortezomib after SC administration in monkeys and humans is given in the table below. The exposure ratio is slightly higher than 1, which is as expected from previous IV studies with bortezomib.

Table 3 – Plasma exposure (AUC in ng.h/ml) comparison of bortezomib in monkeys and human after SC administration

Species	Dose (mg/m²)	AUC (ng.h/mL)	Exposure ratio
Monkey[a]	1.2	211	-
Human[b]	1.3	195	1.08
Human[c]	1.3	155	1.36

[a] Mean of 3 males and 3 females obtained on Cycle 4, Day 74 (TOX7345[3])
[b] Mean of 10 patients, Study CAN 1004 Module 2.7.2 Summary of Clinical Pharmacology studies
[c] Mean of 17 patients, Study MMY-3021 Module 2.7.2 Summary of Clinical Pharmacology studies

AUC = area under the concentration-versus-time curve; - = not applicable

TOX8394 - 8-Week Subcutaneous Toxicity Study in Cynomolgus Monkeys

In this study, Cynomolgus monkeys received SC administration of Velcade once a day for 5 consecutive days during Weeks 1 through 8.

Repeated, once-daily, five times per week subcutaneous administration of Velcade was well tolerated by Cynomolgus monkeys for eight weeks. All monkeys survived to scheduled sacrifice.

Analysis of plasma Velcade concentrations and blood 20S Proteasome activity showed that the time of maximum concentration (Tmax) of plasma Velcade typically occurred within 7 to 15 minutes of dosing, or at 30 minutes post dose if this was the first post dose sampling in the series. Maximum 20S Proteasome inhibition typically occurred 15 to 113 minutes after the observed Tmax. Peak concentrations (Cmax) and exposures (AUC) to Velcade in cynomolgus monkeys increased greater than dose proportionally at the low to mid dose levels and were generally dose proportional at the mid to high dose levels. Mean area under the effect-time curve for 20S Proteasome inhibition was less than dose proportional. There was evidence of accumulation at all dose levels after 8 weeks of dosing.

Subcutaneous administration of Velcade at ≥ 0.0166 mg/kg/dose resulted in decreased platelets and increased mean platelet volume, erythema and oedema at the injection site, soft and liquid stool, and increased urine creatinine, inorganic phosphorus, and sodium.

Subcutaneous administration of Velcade at ≥ 0.0333 mg/kg/dose resulted in decreased food consumption, soft and liquid stool, and lesions in the kidney, pancreas, prostate, spinal cord and peripheral nerves, and initial body weight loss that in most cases was followed by body weight gain during the course of treatment.

At the high dose of 0.05 mg/kg/dose, histopathologic lesions were observed at the injection site, spinal cord, and peripheral nerves, and kidney weights were higher than controls.

Under conditions of the study and based on the available data, the No Observed Adverse Effect Level (NOAEL) for repeated, five times weekly subcutaneous administration of Velcade to cynomolgus monkeys for 8 weeks cannot be identified. The maximum tolerated dose (MTD) was considered to be the highest dose, 0.05 mg/kg/dose.

Local Tolerance

Local tolerability / tissue reaction of Velcade following a single subcutaneous injection was studied in female New-Zealand White rabbits (Study TOX6863).

The administered dose was 0.1 mg/kg body weight (1.2 mg/m^2) at two different concentrations 3.5 mg/ml and 1.0 mg/ml to female New-Zealand White rabbits. Clinical observations for signs of toxicity or irritation at the injection sites were made daily. Necropsies were performed on all rabbits on study days 1 and 4. The injection sites and surrounding tissues from each rabbit were dissected and examined macroscopically and histopathologically.

The dose selection for the present study was based upon information of a previously conducted local tissue irritation study with Bortezomib administered to male New Zealand white rabbits.

In that study, the local tissue reaction of 0.1 mg/kg body weight (1.2 mg/m^2) bortezomib at the clinical concentration of 1.0 mg/ml was evaluated following a single injection either via IV, perivascular (PV), SC or intramuscular (IM) routes. Results indicated no tissue reaction after SC administration.

Based upon the above, it was decided to set the dose at 0.1 mg/kg body weight (1.2 mg/m^2) at two different concentrations, 3.5 mg/ml as the expected concentration in the human SC clinical trials and 1.0 mg/ml as in the current clinical IV concentration.

Gross pathological signs seen at the bortezomib and vehicle injection sites were slight to marked subcutaneous haemorrhages in a few rabbits mainly related to the injection procedure. Oedema noted at the bortezomib injection site of one rabbit dosed with bortezomib concentration 1.0 mg/ml and sacrificed 3 days after injection was considered test article related.

Histopathological examination revealed minimal reaction in the bortezomib injection site of 4 out of 12 female rabbits that were subcutaneously injected with 0.1 mg/kg body weight at a concentration of 3.5 or 1.0 mg/ml and killed respectively 1 or 3 days after injection.

1.3.4. Ecotoxicity/environmental risk assessment

The environmental impact of bortezomib as active pharmaceutical ingredient was presented according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00).

A first estimate of the Predicted Environmental Concentration (PEC) of bortezomib in surface waters receiving the discharge of sewage treatment was calculated and then refined with estimation for the market penetration of the medicinal product in the EU. Based on these calculations, the $PEC_{surfacewater}$ of bortezomib was 0.0000039 µg/L.

As the PECsurfacewater was orders of magnitude below the threshold value of 0.01 µg/L, no further testing in the aquatic environment was required. Consequently, bortezomib and/or its metabolites are unlikely to represent a risk to the environment following prescribed usage in patients.

1.3.5. Discussion on non-clinical aspects

In 2 studies a higher systemic exposure following SC administration compared to IV one at the same dose, was observed. The reason for the higher systemic exposure following SC administration is unknown. However, the issue may be considered solved as human PK data do not confirm the anomaly.

A similar degree of proteasome inhibition (expressed as maximal proteasome inhibition or AUE) was reached after SC or IV administration of bortezomib.

Four toxicology studies were performed: Either single (rabbit) or repeat (Cynomolgus monkeys) administration studies. The duration of the repeated-dose toxicity studies were related to the duration, therapeutic indication and scope of the proposed clinical trial that is: administrations at days 1, 4, 8, and 11 followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.

The limited number of animals used in these studies did not allow the detection of quantitative differences between the IV and SC routes of administration, however, no significant qualitative differences were observed. Clear toxicity signs were evident in monkeys at dose level of 0.166 mg/Kg once weekly for up to 12 weeks. Similar signs were observed with 0.1 mg/Kg for 4 cycles (MTD). The adverse effect profile of VELCADE when administered at 0.166 mg/kg QW for 3 weeks SC was similar to that observed after IV administration.

There was evidence of accumulation at all dose levels after 8 weeks of dosing SC administration.

Safety pharmacology, reprotoxicity, pharmacodynamic drug interactions were discussed in previous submission. No additional studies were performed which was acceptable.

Considering that the number of patients for which the IV route is not recommended and that could take advantage of the SC route is likely to be low, the impact of bortezomib in the environment is not expected to increase due to the new SC route.

1.3.6. Conclusion on the non-clinical aspects

In animal studies, SC and IV administration of bortezomib at a similar dose level (0.1 mg/kg [1.2 mg/m^2]) resulted in comparable pharmacokinetic, pharmacodynamic and toxicological profiles.

No new toxicological findings were noted in non-clinical studies after administration via the SC route.

1.4. Clinical aspects

1.4.1. Introduction

While non-clinical studies showed the oral route of VELCADE administration to be limited by poor bioavailability, the subcutaneous (SC) route was found to be an alternative to intravenous (IV) administration. For some patients, such as elderly or obese patients, where limited or difficult venous access or the need to preserve venous reserves present significant treatment challenges, as well as for patients who may receive prolonged treatment, SC administration was identified as a potentially useful means by which to facilitate care. As a consequence, the MAH conducted studies to support the SC use of Velcade.

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 4 – Overview of Supportive Subcutaneous VELCADE Clinical Studies

Study Number/Title	Study Design	VELCADE/Dexamethasone Treatment Regimen	No. of Subjects Enrolled
Pilot Study 26866138-CAN-1004 Comparison of pharmacokinetics and pharmacodynamics of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma	Phase 1, randomized (1:1), open- label, multicenter study of the PK/PD, safety, and efficacy of SC vs. IV VELCADE in subjects with relapsed multiple myeloma after at least 1 prior therapy.	VELCADE 1.3 mg/m^2 twice weekly by IV bolus or SC injection on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 cycles (24 weeks). VELCADE concentration: 1 mg/mL for both groups Optional oral dexamethasone (20 mg daily on the day of and the day after VELCADE administration) after 2 cycles at investigator's discretion for subjects with stable disease.	24 (12 SC group/ 12 IV group)
Registration Study 26866138-MMY-3021 An open-label, randomized study of subcutaneous and intravenous VELCADE® in subjects with previously treated multiple myeloma	Phase 3, randomized (2:1), open-label, international, multicenter study comparing efficacy, safety and PK/PD of SC vs. IV VELCADE in subjects with relapsed multiple myeloma following 1 to 3 prior lines of therapy	VELCADE 1.3 mg/m^2 twice weekly by IV bolus or SC injection on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 cycles (24 weeks). VELCADE concentration: 1 mg/mL (IV) or 2.5 mg/mL (SC). Optional oral dexamethasone (20 mg daily on the day of and the day after VELCADE administration) beginning in Cycle 5 in case of NC or PR.	222 (148 SC group/ 74 IV group)

IV=intravenous; No. =number; NC=no change; PD=pharmacodynamic; PK=pharmacokinetic; PR=partial response; SC=subcutaneous

1.4.2. Pharmacokinetics

Pharmacokinetic of bortezomib following SC relative to IV administration was studied in 51 subjects (27 subjects in SC and 24 subjects in IV) participating to the 2 studies mentioned in the above table.

For both studies, bortezomib plasma samples were analyzed in a central laboratory (Tandem Labs, West Trenton, NJ, USA) using a validated liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS) assay.

For both studies, the following main PK parameters were estimated from blood samples obtained from subjects administered VELCADE through the IV and SC route:

- Cmax – maximum observed plasma concentration
- C0 – initial concentration extrapolated to time zero after an IV dose
- tmax – time of maximum plasma concentration

- AUClast - the area under the plasma concentration-time curve from time 0 to the last measurable concentration
- AUC∞ - the area under the plasma concentration-time curve from time 0 to infinity
- t1/2 – apparent terminal half-life, computed as (ln2/ke) where ke is the slope of the terminal log-linear phase of the plasma concentration-time curve.

The PK parameters were calculated using conventional non-compartmental methods using actual times of blood sampling and for the statistical analysis:

- the PK parameters are presented by arithmetic mean ± standard deviation (SD) for the individual treatments;
- Tmax values were present as median (range).
- Pair-wise comparison between 2 treatments for Cmax and AUC values are based on log-transformed data.

Absorption

Study CAN-1004 was a randomized, Phase 1 pilot study that first compared the pharmacokinetics, pharmacodynamics, safety, tolerability, and efficacy of single-agent SC and IV VELCADE in 24 subjects (20 evaluable for pharmacokinetic analyses) with relapsed multiple myeloma. The subject population, dose and schedule of VELCADE administration (1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 3-week cycle), and duration of therapy (up to 8 cycles) were consistent with the approved recommendation at that time. For SC administration, Velcade was injected in the thigh or abdomen. Twenty subjects (10 IV and 10 SC) were evaluable for PK analysis.

The study was performed in target population. Out of the 24 subjects enrolled in the study, 10 (10 of 24; 42%) were men and 14 (14 of 24; 58%) were women. Mean body weight was 69 kg in the IV group versus 71 kg in the SC group. The mean age was 60.4 years with 18 subjects (18 of 24; 75%) being less than 65 years.

Twenty subjects (10 IV and 10 SC) were evaluable for PK analysis. Blood samples for PK and PD analyses were collected on Days 1 and 11 of Cycle 1 at the following time-points: 30 min before VELCADE administration, and at 2, 5, 15, 30, and 60 min, and 2, 4, 6, 10, 24, 48, and 72 hours after VELCADE administration.

Time course of bortezomib in plasma after IV or SC administration of 1.3 mg/m2 on Days 1 and 11 of Cycle 1 are shown in the following figures.

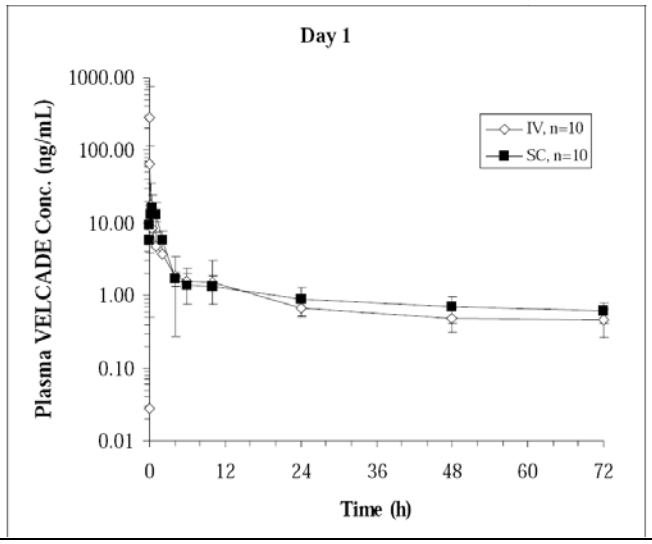

Figure 1 - Mean Plasma Concentration-Time Profile of Velcade Following SC and IV administration on Day 1

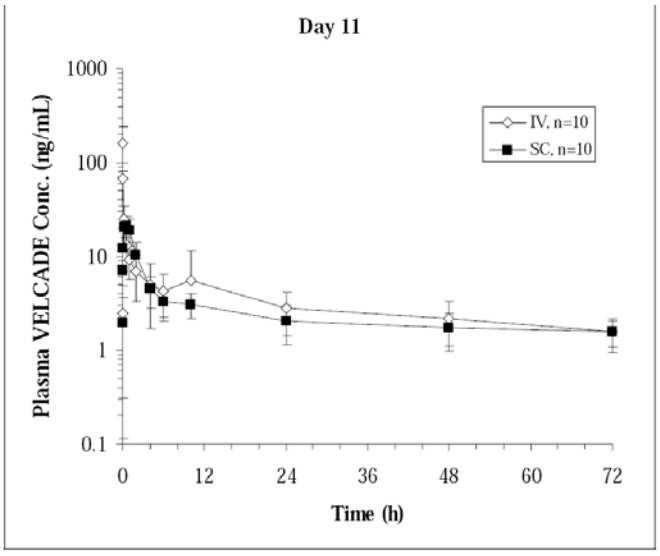

Figure 2 - Mean Plasma Concentration-Time Profile of Velcade Following SC and IV administration on Day 11

PK parameters are shown in the following table:

Table 5 – Summary of Bortezomib Pharmacokinetic Parameters Following Intravenous or Subcutaneous Administration of VELCADE 1.3 mg/m^2 on Days 1 and 11 of Cycle 1 (Study CAN-1004)

	Day 1		Day 11	
Parameter	IV (n=10)	SC (n=10)	IV (n=10)	SC (n=10)
C_{max} (ng/mL)	286 (466)	16.5 (8.35)	162 (79.9)	22.5 (5.36)
T_{max} (h)[a]	0.03 (0.03-0.05)	0.53 (0.30-1.02)	0.03 (0.03-0.50)	0.5 (0.25-1.00)
AUC_{last} (ng.h/mL)	104 (99.0)	92.1 (17.8)	241 (82.0)	195 (51.2)

AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of last quantifiable time point; C_{max}=maximum observed plasma concentration; h=hours; IV=intravenous; SC=subcutaneous; T_{max}=time when C_{max} is first observed
Values are Mean (standard deviation)
[a] Median (range)

Table 6 – Summary of Analysis for Pharmacokinetic Parameters (Study CAN-1004)

			SC		IV		SC-IV		
Day	Type	Parameter	N	LS mean	N	LS mean	Diff.	95% CI	p-value
1	Plasma	C_{max}	10	2.7	10	5.1	-2.4	(-3.04,-1.81)	<0.001
1	Plasma	AUC_{∞}	10	5.0	10	5.0	0.0	(-0.50,0.49)	0.979
1	Plasma	AUC_{last}	10	4.5	10	4.4	0.1	(-0.33,0.46)	0.738
11	Plasma	C_{max}	10	3.1	10	4.9	-1.8	(-2.38,-1.21)	<0.001
11	Plasma	AUC_{∞}	10	6.0	10	5.9	0.0	(-0.34,0.41)	0.865
11	Plasma	AUC_{last}	10	5.2	10	5.4	-0.2	(-0.47,0.10)	0.187

There was a high degree of inter-subject variability (based on %CV) in:

- mean plasma Cmax values of VELCADE for both routes of administrations (i.v., %CV = 63.3; s.c., %CV= 50.5);
- AUClast (area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration): 95.0% for i.v. and 19.4% for s.c.;
- AUC∞ (area under the plasma concentration-time curve from time zero to infinite time): 86.2% for i.v. and 35.4% for s.c.;
- mean terminal half-life values that were 98.1 hours and 65.7 hours for the i.v. and s.c. groups, respectively(%CV=147.8 and 70.7 for the i.v. and s.c. groups, respectively).

Study MMY-3021 was a Phase 3, randomized, open-label, multicenter, international, prospective study demonstrating the comparable efficacy, pharmacokinetics, pharmacodynamics, safety, and tolerability, of single-agent IV and SC VELCADE in subjects with relapsed multiple myeloma after prior systemic therapy.

A substudy of 31 subjects from Study MMY-3021 was conducted to investigate the pharmacokinetic and pharmacodynamic characteristics of IV and SC VELCADE administration.

The study was performed in target population. The proportion of males to females in the SC treatment group was equal (50%), there were more males (64%) versus females (36%) in the IV treatment group. In both the SC and IV treatment groups the median age was 64.5 years (range: 38 to 88), with 50% of subjects less than 65 years of age and 50% of subjects 65 years of age or older.

Subjects were randomized to receive VELCADE 1.3 mg/m^2 administered by SC injection or IV injection on Days 1, 4, 8, and 11 of a 3 week cycle for 8 cycles.

In order to minimize VELCADE SC injected solution, a concentration of 2.5 mg/mL bortezomib was used for SC administration rather than the standard concentration of 1 mg/mL for IV administration.

Potential SC injection sites were abdomen (right or left) and thighs (right or left) and it was recommended to rotate SC injection sites within a treatment cycle.

Blood samples for PK and PD analyses were collected on Day 1 predose and on Day 11 of Cycle 1 at the following time-points: 0 hour (immediately before dosing), and at 2, 5, 15, and 30 minutes, and at 1, 2, 4, 6, 10, 24, 32, 48, and 72 hours after VELCADE administration on Day 11.

Time courses of bortezomib in plasma after IV or SC administration of 1.3 mg/m2 on Day 11 of Cycle 1 are shown in the following figure.

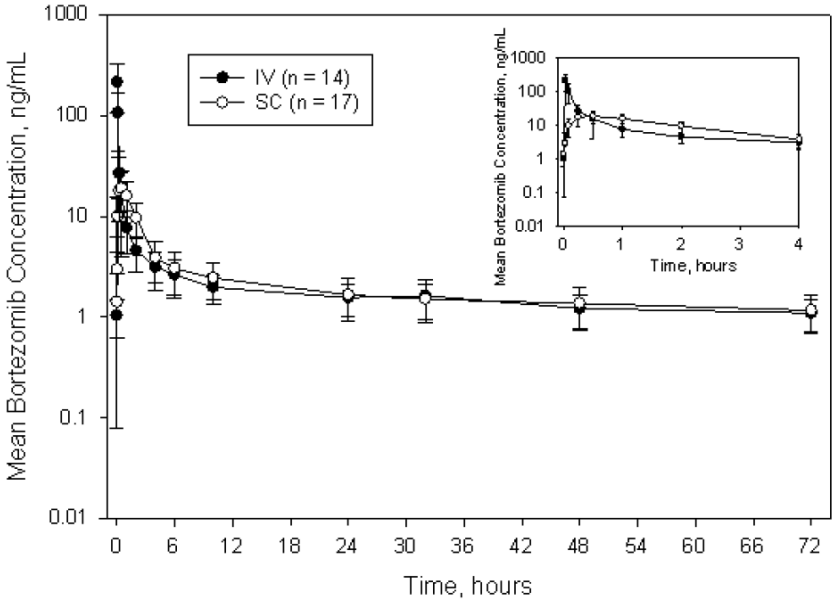

Figure 3 - Mean (SD) Plasma Bortezomib Concentration-Time Profile Following Intravenous or Subcutaneous Injection of VELCADE 1.3 mg/m^2 on Day 11 (Log:Linear Scale; Study MMY-3021)

PK parameters were the following:

Table 7 – Summary of Bortezomib Pharmacokinetic Parameters Following Intravenous or Subcutaneous Administration of VELCADE 1.3 mg/m2 on Day 11 of Cycle 1 (Study MMY-3021)

	Treatment	
Parameter	IV (N=14)	SC (N=17)
C_{max} (ng/mL)	223 (101)	20.4 (8.87)
T_{max} (h)[a]	0.03 (0.03 – 0.08)	0.50 (0.08-1.00)
AUC_{last} (ng.h/mL)	151 (42.9)	155 (56.8)

AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of last quantifiable time point; C_{max}=maximum observed plasma concentration; h=hours; IV=intravenous; SC=subcutaneous; T_{max}=time when C_{max} is first observed
Values are Mean (standard deviation)
[a] Median (range)

AUC following SC injection was equivalent to that of the IV injection with a geometric mean ratio (SC to IV) of 0.992 and 90% CI of 80.18% to 122.80%; ie, within the standard 80% – 125% bioequivalence criteria.

Effect of Concentration of Injected Solution

In study MMY-3021, bortezomib was reconstituted to a concentration of 2.5 mg/mL for SC administration. In study CAN-1004, bortezomib was injected subcutaneously in a concentration of 1 mg/mL, thus a higher volume was injected subcutaneously according to the posology scheduled 1.3 mg/m^2.

The pharmacokinetic and PD parameters of the SC administration were comparable between the 2 studies as indicated in the table below. Thus, the volume of the SC injected solution does not appear to influence bortezomib pharmacokinetics or PD.

Table 8 – Summary of Pharmacokinetic and Pharmacodynamic Parameters Following Subcutaneous Injections of VELCADE 1.3 mg/m^2 Using 2.5 mg/ml and 1.0 mg/ml Solutions

Parameter	2.5 mg/mL[a]	1.0 mg/mL[b]
C_{max} (ng/mL)[c]	20.4 (8.87)	22.5 (5.36)
T_{max} (h)[d]	0.5 (0.08-1.00)	0.5 (0.25-1.00)
AUC_{last} (ng.h/mL)[c]	155 (56.8)	195 (51.2)
AUE_{72} (%.h)[c]	1714 (617)	1619 (804)
E_{max} (%)[c]	63.7 (10.6)	57.0 (12.8)

AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of last quantifiable time point; AUE_{72}=area under the percent inhibition-time curve from time 0 to 72 hours; E_{max}=observed maximum percent inhibition of 20S proteasome activity (ChT:T); h=hours; SD=standard deviation; T_{max}=time when C_{max} is observed
[a] 26866138-MMY-3021
[b] 26866138-CAN-1004
[c] Mean (SD)
[d] Median (range)

Distribution

In **study CAN-1004**, systemic exposure following single dose was measured by calculating individual and mean AUClast (104 ng.h/mL and 92.1 ng.h/mL, for the i.v. and s.c. groups, respectively) and AUC∞ values (183 ng.h/mL and 151 ng.h/mL, for the i.v. and s.c. groups, respectively). There was a similarity between both mean AUCs when compared across both routes of administrations.

The mean pseudo-steady state volume of distribution was relatively high (Vd =1636 L and Vd/F = 1330 L, for i.v. and s.c. groups, respectively), indicating extensive distribution into peripheral tissues.

An increase in the systemic exposure to VELCADE was observed following multiple dose administration (Day 11) consistent with similar observations from previous studies. This was particularly evident from a comparison of the plasma AUClast values, where higher mean values were observed after administration on Day 11 than after Day 1 for both the i.v. (241 ng.h/mL) and s.c. (195 ng.h/ml) routes of administrations.

Distribution values were not calculated in **Study MMY-3021**.

Elimination

VELCADE exhibited similar total systemic clearance following single dose administration in **Study CAN-1004** (mean CL = 17.9 L/h and mean CL/F = 16.6 L/h for the i.v. and s.c. groups, respectively).

The mean terminal half-life values were 98.1 hours and 65.7 hours for the i.v. and s.c. groups, respectively, with a high degree of inter-subject variability (%CV=147.8 and 70.7 for the i.v. and s.c. groups, respectively).

Lower mean clearance values were observed after repeat administration. As expected, a clear statistically significant difference was apparent upon assessment of the mean plasma Cmax values after s.c. administration compared with i.v. administration.

Elimination values were not calculated in **Study MMY-3021**.

1.4.3. Pharmacodynamics

For both CAN-1004 and MMY-3021 studies, whole blood samples were analyzed to determine the chymotryptic activity of the proteasome, using an established method based on a fluorometric measurement of the rate at which the proteasome hydrolyzes an amide bond in a small peptide substrate.

Analysis of proteasome inhibition was performed on the change in proteasome activity from baseline of the first dose (Day 1 of Cycle 1) to subsequent time points. The activity was normalized to the amount of protein present in each sample. Actual blood sampling times relative to study medication administration was used for the analyses.

The following VELCADE plasma PD parameters were estimated:

- Emax– Observed maximum percent inhibition of 20S proteasome activity, taken directly from the inhibition-time profile
- tmax – Time when Emax is observed, taken directly from the inhibition-time profile
- AUElast – Area under the percent inhibition-time curve from time 0 to the last sampling time point (72h), 72 hours, calculated by linear trapezoidal summation

Study CAN-1004

Pharmacodynamic samples were to be taken at the following 13 scheduled times for each VELCADE treatment group, on Day 1 and Day 11 of the first cycle.

As seen in the figure below, there was similar inhibition due to VELCADE on Day 1 and Day 11 within each of the SC and IV routes of administrations. Overall, there was marginally higher maximal inhibition (based on Emax only) after IV administration compared with SC administration. For most subjects, the variability as depicted by standard deviations was relatively higher at time points later than 24 hours.

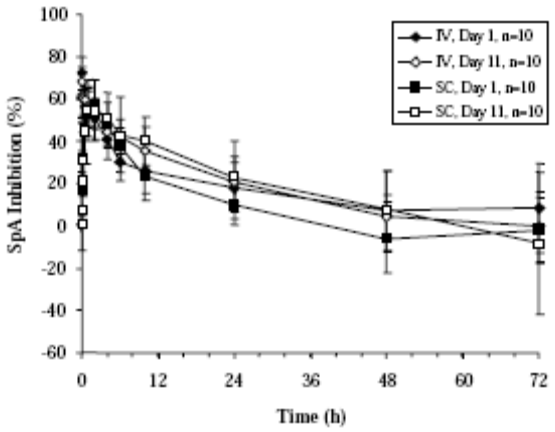

Figure 4 - Mean (SD) Whole Blood 20S Proteasome Specific Activity (SpA) inhibition-Time Profile of Velcade Following IV and SC administration as measured on Day 1 and Day 11

After single dose

In general, PD activity declined over a 72-hour period, in most cases 12 hours after VELCADE administration with mean proteasome inhibition values ranging 20% to 40%, for both treatment groups.

Inter−subject variability range was 30% or less (expressed as coefficient of variation, %CV) during the first 12 hours after dosing, whereas variability was higher at subsequent sampling time points after dosing (range, 35% - 256%) for both treatment groups on Day 1 and Day 11.

There were no statistically significant differences (p-value = 0.11 on Day 1) in the mean area under the effect-time curve (AUE) of VELCADE for SC compared with IV administration on Day 1.

After repeat dose

There were no statistically significant differences (p-value = 0.64 on Day 11) in mean AUE of VELCADE for both treatments after multiple dosing. As would be expected, mean maximum inhibition values on Day 11 were 68.8 % (6.49%) for the IV group and 57.0 % (12.8%) for the SC group; this difference was statistically significant (p-value = 0.022). Upon qualitative assessment, no differences in the mean pharmacodynamic parameter plots for the two treatment groups were observed.

In general, there was higher variability observed between Day 1 and Day 11 mean values in the SC group compared with the IV group. Nevertheless, across both groups, no significant impact on proteasome inhibition by VELCADE was noticed after either SC or IV administration.

Study MMY-3021

Blood samples were analyzed for 20S proteasome specific activity using a qualified kinetic fluorescence detection method. All 31 subjects who participated in the pharmacokinetic portion of this study were included in the pharmacodynamic analysis.

The mean maximum percent inhibition of proteasome activity (Emax) was comparable for the SC and IV treatment groups (63.7% vs. 69.3%; respectively) following multiple 1.3 mg/m^2 SC or IV doses of VELCADE (Table 9).

Table 9 – Summary of Bortezomib Pharmacodynamic Parameters Following Intravenous or Subcutaneous Administration of VELCADE 1.3 mg/m^2 on Day 11 of Cycle 1 (Study MMY-3021 pharmacodynamic analysis set)

Parameter	IV (N=14)	SC (N=17)
T_{max} (h)[a]	0.08 (0.03-0.5)	2.00 (0.5-24)
E_{max} (%)[b]	69.3 (13.2)	63.7 (10.6)
AUE_{72} (h.%)[b]	1383 (767)	1714 (617)

AUE_{72}=area under the percent inhibition-time curve from time 0 to 72 hours; E_{max}=observed maximum percent inhibition of 20S proteasome activity (ChT:T); h=hours; IV=intravenous; SC=subcutaneous; SD=standard deviation; T_{max}=time when E_{max} is observed

[a] Median (range)

[b] Mean (SD)

Median Tmax was approximately 5 minutes for the IV treatment group and 2 hours for the SC treatment group. Mean AUE72 following SC injection was comparable to that of the IV injection and within the observed variability (CV 36 - 55%).

The protocol recommended rotation of SC injections sites between the abdomen (left and right) and the thigh (left and right). There were no apparent PD differences related to the site of injection as Emax, Tmax, and AUE72 following SC injection in the abdomen were comparable to those in the thigh.

1.4.4. Discussion on clinical pharmacology

Studies supporting the SC administration were correctly designed and performed. Data from 51 subjects (27 subjects in SC and 24 subjects in IV - pooled: 20 from study CAN-1004 and 31 from study MMY-3021), were obtained and analysed.

The pharmacokinetic and PD parameters of the SC administration were comparable between the 2 studies CAN-1004 and MMY-3021. Systemic exposure (AUC) was similar after both SC and IV administration. As expected, Cmax was markedly lower after SC administration.

In the CAN-1004 study maximum plasma bortezomib concentration (Cmax) was lower (94% lower on Day 1 and 86% lower on Day 11) than the IV Cmax, and occurred later with Tmax of 30 minutes for SC administration and a Tmax of approximately 5 min for the IV route. The difference in exposure in terms of Cmax was short-lasting. A slight increase in exposure following the SC administration relative to the IV administration was observed for about 4 hours post dosing. The total systemic exposure to Bortezomid was similar following SC or IV injection (mean AUClast = 155 (SC) vs. 151 (IV) ng.h/mL) showing that the original peak observed after IV injection did not have any impact on AUClast following SC or IV injection. The equivalent bortezomib total systemic exposure following SC and IV injections was translated into comparable efficacy results between the 2 routes of administrations.

Accumulation (AUC day 11/AUC day 1) was also very similar for both routes.

PD effect, measured as maximum proteasome inhibition (Emax) and the area under the effect time curve for proteasome inhibition (AUE) were comparable between the SC and IV routes.

In the MMY-3021 study, the mean Emax was comparable for the SC and IV groups. Mean AUE72 following SC injection was comparable to that of the IV injection and within the observed variability (CV = 36 - 55%).

The site of SC injection (abdomen or thigh) and the volume of the injected solution (1mg/ml CAN-1004, or 2.5 mg/ml MMY-3021) did not affect significantly PK or PD parameters. Also, Emax and AUE72 were comparable.

Overall results of the two studies clearly show that systemic exposure and PD effect are similar after both SC and IV administrations.

No new studies were aimed to assess drug-drug interactions. Based on bortezomib equivalent systemic exposure following the SC route relative to the IV route, the results of all completed bortezomib clinical pharmacology IV studies with drugs that may alter bortezomib metabolism such as ketoconazole (strong CYP 3A4 inhibitor), omeprazole (CYP 2C19 inhibitor), rifampicin (strong CYP3A4 inducer), dexamethasone (a relatively weak CYP 3A4 inducer), melphalan, and prednisone are also applicable to the SC route of administration.

1.4.5. Conclusions on clinical pharmacology

Clinical pharmacology data demonstrated that systemic exposure and PD effect were similar after both SC and IV administration, thus supporting the SC route of administration. The site of SC injection (abdomen or thigh) and the volume of the injected solution (1mg/ml CAN-1004, or 2.5 mg/ml MMY-3021) did not significantly affect PK or PD parameters.

1.5. Clinical efficacy

1.5.1. Dose response study(ies)

In the two clinical studies submitted, the same dosage schedule was used according to the approved Velcade, i.e. 1.3 mg/m2 twice weekly by IV bolus or SC injection on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 cycles (24 weeks).

In study CAN-1004, VELCADE concentration was 1 mg/ml for both groups IV and SC.

In order to reduce the volume of subcutaneously injected VELCADE in Study MMY-3021, each vial of VELCADE was to be reconstituted in 1.4 mL of normal saline, for a final concentration of 2.5 mg/mL rather than the concentration of 1.0 mg/mL used for IV administration. The use of a 2.5 mg/mL concentration was supported by data from a rabbit tolerability study in which minimal reaction was observed at the VELCADE-treated injection site of female rabbits that were injected SC with 0.1 mg/kg body weight at a concentration of 3.5 mg/mL or 1.0 mg/mL.

1.5.2. Main study MMY-3021

Methods

Study MMY-3021 was a randomized, open-label, Phase 3, non-inferiority study that compared the safety and efficacy of VELCADE administered by either the IV and SC route in 222 subjects with progressive disease who had received 1 to 3 prior lines of therapy (previous treatment with Velcade was an exclusion criterion) and had measurable disease and evidence of disease progression since their last previous therapy for multiple myeloma. As discussed before, a substudy of 31 subjects from

Study MMY-3021 was also conducted to investigate the pharmacokinetic and pharmacodynamic characteristics of IV and SC VELCADE administration.

The study consisted of 3 phases: a screening phase (21 days), an open-label treatment phase of 24 weeks (Subjects were to receive VELCADE on Days 1, 4, 8, and 11 of a 3-week cycle for 8 cycles) and a post-treatment follow-up phase.

Study Participants

The study protocol required randomisation of not less than 216 subjects with multiple myeloma who had received 1 to 3 prior lines of therapy and had measurable evidence of progression disease since their last previous therapy were planned for enrollment in the study.

Inclusion criteria were the following:

- Men or women aged 18 years or older
- Diagnosis of multiple myeloma based on the standard criteria described in Attachment 1
- Measurable, secretory multiple myeloma defined as serum monoclonal immunoglobulin G (IgG) of ≥10 g/L, serum monoclonal immunoglobulin A (IgA) or immunoglobulin E (IgE) of ≥5 g/L, or serum monoclonal immunoglobulin D (IgD) of ≥0.5 g/L; or urine M-protein of ≥200 mg/24 hours
- Relapse or progression of myeloma following prior systemic antineoplastic therapy.
- Karnofsky Performance Status (KPS) score ≥70%
- Platelet count ≥50 x 109/L without transfusion support within 7 days before the laboratory test
- Hemoglobin ≥8 g/dL (≥4.96 mmol/L) without transfusion support within 7 days before the laboratory test
- Absolute neutrophil count (ANC) ≥0.75 x 109/L
- Corrected serum calcium <14 mg/dL (<3.5 mmol/L)
- Aspartate aminotransferase (AST) ≤2.5 times upper limit of normal (ULN)
- Alanine aminotransferase (ALT) ≤2.5 times ULN
- Total bilirubin ≤1.5 times ULN (except in subjects with congenital bilirubinemia, such as Gilbert syndrome)
- Creatinine clearance ≥20 mL/min, calculated using the formula in Attachment 3
- Toxic effects of previous therapy or surgery had resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 3.0) Grade 1 or better
- Women who were not postmenopausal or surgically sterile were to have had a negative pregnancy test and were to have agreed to use an acceptable method of birth control during the study until 30 days after the last dose of study drug.
- Men were to have agreed to not father a child and to use a latex condom during treatment and for 30 days after the last dose of study drug, even if they had had a successful vasectomy, if their partners were of childbearing potential.
- Voluntary written informed consent was to be given before performance of any study-related procedure not part of normal medical care, with the understanding that consent could be withdrawn by the subject at any time without prejudice to future medical care.

Amongst exclusion criteria were previous treatment with VELCADE, more than 3 previous lines of therapy, Peripheral neuropathy.

Treatments

VELCADE was administered at its approved dose and schedule (1.3 mg/m^2 on Days 1, 4, 8, and 11 of every 3-week cycle) for 8 cycles in both treatment groups. Concomitant dexamethasone administration was permitted during Cycles 5 to 8 for subjects who, after Cycle 4, had a documented suboptimal response (no change or partial response [PR]). Dexamethasone, was given 20 mg orally on the day of and the day after VELCADE administration (Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle).

Dose modifications of VELCADE or dexamethasone could be made as necessary, according to the protocol-specified dose adjustment guidelines. Subjects with progressive disease (PD) were to discontinue treatment at the time that PD was confirmed. Subjects who withdrew from treatment for reasons other than progressive disease were to continue to undergo efficacy assessments for the duration of the treatment phase or until documentation of progressive disease.

In the post-treatment follow-up phase, subjects who had not progressed were to be assessed every 8 weeks until PD was recorded. After PD, subjects were to be assessed every 12 weeks for survival and subsequent therapies. Follow-up was to continue until the end of the study, which was defined as 1 year after the last subject was randomised.

Objectives

The primary objective of Study MMY-3021 was to compare the ORR, defined as the proportion of subjects with CR or PR after 4 cycles of subcutaneously administered VELCADE and intravenously administered VELCADE in subjects with previously treated multiple myeloma.

The secondary objectives of the study were:

- To determine the complete response (CR), near complete response (nCR), and very good partial response (VGPR) rates after 4 cycles of single-agent VELCADE, the ORR after 8 cycles including the effect of adding dexamethasone, the duration of response, time to progression (TTP), progression-free survival (PFS), 1-year survival, and time to response following VELCADE treatment, administered either SC or IV.
- To evaluate the safety and tolerability of the 2 routes of administration, including the local tolerability of SC administration.
- To describe the plasma pharmacokinetics and pharmacodynamics (via 20S proteasome inhibition assay in whole blood) of subcutaneously administered VELCADE compared with intravenously administered VELCADE.

Exploratory objectives of the study were:

- To assess medical resource utilization data specifically related to the diagnosis and treatment of any complications related to either the SC or IV route of administration was to be collected.
- To determine the feasibility of detecting baseline proteasome activity levels in bone marrow in a subset of subjects.

Outcomes/endpoints

Disease response was measured according to the modified European Group for Blood and Marrow Transplantation (EBMT) criteria, with the addition of the PR subcategories of nCR and VGPR.

Primary endpoint

Non-inferiority was defined as retaining 60% of the IV (active control) treatment effect as measured by ORR (CR+PR rate after 4 cycles of Velcade prior to the addition of dexamethasone).

Secondary endpoints

- CR, nCR, and VGPR after 4 cycles (prior to the addition of dexamethasone); definitions of each response are described in, Assessment of Progressive Disease and Disease Response ORR (CR + PR) after 8 cycles (including the addition of dexamethasone).

- Duration of response, defined as the time from the date of first documentation of a confirmed CR or PR (overall cycles) to the date of first documented PD. Responders without PD were to be censored at the date of the last clinical assessment of response.
- TTP, defined as the time from the date of randomization to the date of first documentation of PD or relapse from CR, whichever occurred earlier. Subjects who had not progressed were to be censored at the date of the last clinical assessment of response.
- PFS, defined as the time from the date of randomization to the date of first documented PD, relapse from CR, or death due to any cause, whichever occurred earlier. Subjects who had not progressed and were alive on the cut-off date for analysis were to be censored at the date of the last clinical assessment of response.
- One-year survival, defined as the survival rate at 1 year after randomization. Survival was measured from the date of randomization to the date of a subject's death. If a subject was alive or the vital status was unknown, the subject was to be censored at the date that he or she was last known to be alive.
- Time to response, defined as the time from the date of randomization to the date of the first documentation of a confirmed CR or PR. Those subjects without confirmed response (CR or PR) were to be censored either at the time of PD or at the last clinical assessment of response.

Evaluations of safety and tolerability included assessments of adverse events, clinical laboratory tests (haematology and serum chemistry), local injection site tolerability, KPS, the FACT/GOG-Ntx questionnaire, physical examination findings, body weight, BSA, and vital sign measurements. An electrocardiogram and chest x-ray were performed during the screening phase and could be repeated during the study as clinically indicated. Additionally, a 12-lead ECG was to be performed during screening and repeated during the study as clinically indicated.

Sample size

The response-evaluable population (145 subjects and 73 subjects in the SC and IV treatment groups, respectively) included subjects who received at least 1 dose of study drug and who had measurable disease at study entry.

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

Randomisation

Subjects were randomly assigned in a 2:1 ratio to receive 1.3 mg/m2 VELCADE by either SC or IV injection: this ratio was chosen because it provides higher statistical power than a 1:1 ratio for the study objective, and also because the safety and efficacy profile of single-agent IV VELCADE in relapsed multiple myeloma had already been well characterized. Moreover, it allowed for the collection of more data for the experimental group with the same total number of subjects enrolled in the study.

Subjects were stratified by the number of lines of prior therapy (1 versus >1) and International Staging System (ISS) stage (incorporating beta2-microglobulin and albumin levels; Stages I, II, or III). The planned total sample size was approximately 216 subjects (144 in the SC treatment group and 72 in the IV treatment group).

Blinding (masking)

This was an open label study, thus no blinding was performed.

Statistical methods

The intent-to-treat (ITT) population was defined as all randomized subjects.

Time-to-event endpoints include time to response, 1-year survival, TTP and PFS. They were to be analyzed using the ITT population as the primary analysis population. The primary endpoint and secondary response-related endpoints were to be analyzed using the response-evaluable population as the primary analysis population.

The response-evaluable population was defined as subjects who received at least 1 dose of study drug and had measurable, secretory multiple myeloma, defined as a serum monoclonal IgG or IgM of ≥10 g/L or a serum monoclonal IgA or IgE ≥5 g/L, or a serum monoclonal IgD of ≥0.5g/L, or urine M-protein of ≥200 mg/24 hours, at study entry.

Subjects were to be categorized by the best response observed after 4 cycles of study drug. The number and percentage of subjects in each response category were to be calculated. The 95% CI around ORR SC - 0.60 ORR IV was to be calculated. To declare non-inferiority, the lower bound of this CI needed to be ≥0. The p value associated with the non-inferiority hypothesis was to be calculated. If non-inferiority was demonstrated, the 95% CI around the difference between the treatment groups (ORRSC - ORRIV) was to subsequently be calculated to assess superiority.

No interim analysis was planned for this study.

Results

Participant flow

Subject disposition is presented in the figure below.

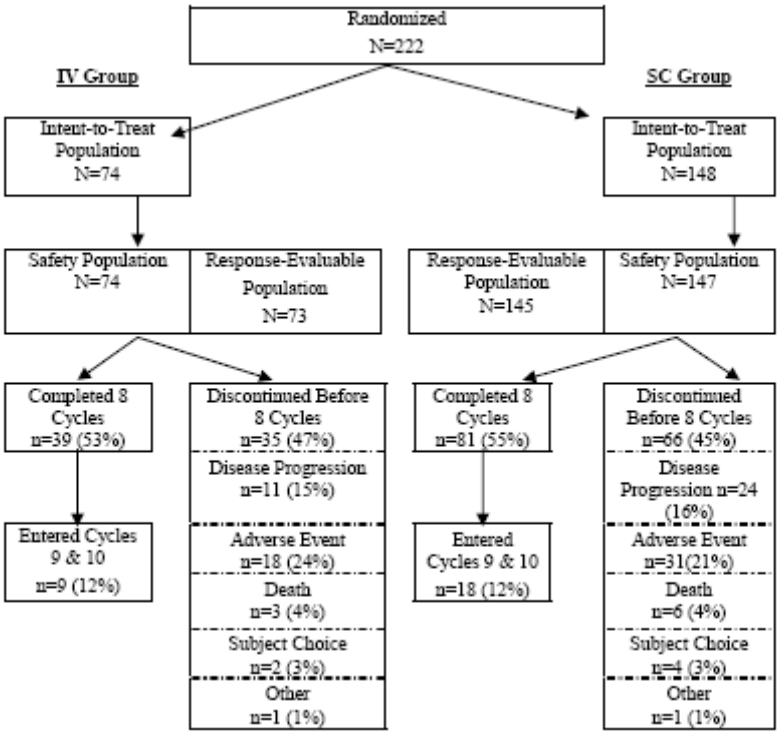

Figure 5 – Subject disposition

Recruitment

First subject enrolled: 16 July 2008. Date last subject enrolled: 26 February 2010. Date of data cut-off: 31 August 2010.

Conduct of the study

There were 2 amendments to the original study protocol dated 14 March 2008.

Baseline data

Demographic and baseline characteristics are presented in the tables below.

Table 10 – Demographic and baseline characteristics (Study MMY-3021 - ITT analysis set)

	----- IV ---- (N=74)	----- SC ---- (N=148)	--- Total --- (N=222)
Age (years)			
N	74	148	222
Category, n (%)			
<65	37 (50)	74 (50)	111 (50)
≥65	37 (50)	74 (50)	111 (50)
Mean (SD)	64.0 (12.11)	64.3 (8.96)	64.2 (10.09)
Median	64.5	64.5	64.5
Range	(38;86)	(42;88)	(38;88)
Sex, n (%)			
N	74	148	222
Male	47 (64)	74 (50)	121 (55)
Female	27 (36)	74 (50)	101 (45)
Race, n (%)			
N	74	148	222
White	71 (96)	143 (97)	214 (96)
Asian	3 (4)	5 (3)	8 (4)
Baseline KPS (%)			
N	74	148	222
Category, n (%)			
70	12 (16)	32 (22)	44 (20)
80	24 (32)	57 (39)	81 (36)
≥90	38 (51)	59 (40)	97 (44)
Mean (SD)	84.6 (8.94)	82.5 (8.72)	83.2 (8.83)
Median	90.0	80.0	80.0
Range	(70;100)	(70;100)	(70;100)

Table 11 –Baseline disease characteristics (Study MMY-3021 - ITT analysis set)

	-------- IV ------- (N=74)	-------- SC ------- (N=148)	------ Total ------ (N=222)
Measurable type as per central lab, n (%)			
N	74	148	222
Secretory	71 (96)	144 (97)	215 (97)
Oligosecretory	3 (4)	4 (3)	7 (3)
Specific myeloma type, n (%)			
N	74	148	222
IgG	53 (72)	96 (65)	149 (67)
- IgG, kappa	40 (54)	64 (43)	104 (47)
- IgG, lambda	13 (18)	32 (22)	45 (20)
IgA	14 (19)	38 (26)	52 (23)
- IgA, kappa	11 (15)	19 (13)	30 (14)
- IgA, lambda	3 (4)	19 (13)	22 (10)
IgD	0	1 (1)	1 (<1)
- IgD, lambda	0	1 (1)	1 (<1)
IgM	1 (1)	1 (1)	2 (1)
- IgM, kappa	1 (1)	1 (1)	2 (1)
Light chain	6 (8)	12 (8)	18 (8)
- kappa	3 (4)	8 (5)	11 (5)
- lambda	3 (4)	4 (3)	7 (3)
ISS staging[a], n (%)			
N	74	148	222
I	20 (27)	40 (27)	60 (27)
II	30 (41)	60 (41)	90 (41)
III	24 (32)	48 (32)	72 (32)
IgG (g/dL) m-protein			
N	53	96	149
Mean (SD)	3.07 (1.839)	3.45 (2.263)	3.32 (2.123)
Median	2.70	2.80	2.80
Range	(0.4;8.5)	(0.0;10.7)	(0.0;10.7)
IgA (g/dL) m-protein			
N	14	38	52
Mean (SD)	2.34 (1.282)	2.65 (1.890)	2.57 (1.740)
Median	2.05	2.35	2.25
Range	(0.9;5.3)	(0.0;8.4)	(0.0;8.4)
Urine m-protein (mg/24hr)			
N	74	148	222
Mean (SD)	195.94 (481.543)	348.50 (1017.710)	297.65 (877.906)
Median	0.00	0.00	0.00
Range	(0.0;2508.1)	(0.0;10310)	(0.0;10310)

Type of measurable myeloma and specific type are derived based on central lab data.
[a] ISS Staging is derived from baseline central laboratory data.
Urine m-protein is summarized for all subjects with available values.

Numbers analysed

One hundred and forty-seven subjects in the SC treatment group and 74 subjects in the IV treatment group are included in the safety analysis dataset. This dataset includes all randomized subjects who received at least 1 dose of study drug. One non-treated subject was excluded from the safety analysis. Study treatment is summarised in the table below.

Table 12 – Summary of Study Treatment (Study MMY-3021 - Safety analysis set)

	IV (N=74)	SC (N=147)
Number of treatment cycles[a]		
N	74	147
Mean (SD)	6.1 (2.77)	6.4 (2.71)
Median	8.0	8.0
Range	(1;10)	(1;10)
Time on study treatment (weeks)		
N	74	147
Mean (SD)	17.52 (8.800)	18.07 (8.568)
Median	22.57	22.57
Range	(0.6;30.7)	(0.1;33.1)
VELCADE dose intensity (cycles 1-4) mg/m^2/cycle[b]		
N	74	147
Mean (SD)	4.70 (0.664)	4.83 (0.645)
Median	4.89	5.13
Range	(2.4;5.4)	(1.2;5.3)
VELCADE dose intensity (cycles ≥5) mg/m^2/cycle[b]		
N	48	105
Mean (SD)	4.35 (1.078)	4.41 (1.048)
Median	4.91	4.88
Range	(1.4;5.5)	(1.3;5.3)
VELCADE relative dose intensity (cycles 1-4)[c]		
N	74	147
Mean (SD)	0.904 (0.1276)	0.930 (0.1240)
Median	0.940	0.987
Range	(0.45;1.04)	(0.24;1.02)
VELCADE relative dose intensity (cycles ≥5)[c]		
N	48	105
Mean (SD)	0.837 (0.2073)	0.848 (0.2015)
Median	0.944	0.938
Range	(0.27;1.05)	(0.25;1.02)
Subjects who received dexamethasone, n (%)		
N	74	147
Yes	39 (53)	82 (56)
No	35 (47)	65 (44)
Dexamethasone dose intensity mg/cycle		
N	39	82
Mean (SD)	149.20 (22.459)	148.00 (23.940)
Median	160.00	160.00
Range	(72.0;160.0)	(40.0;163.3)

[a] Number of treatment cycles = last cycle dosed - first cycle dosed + 1.

[b] Dose intensity (mg/m^2/cycle) is calculated as the sum of total doses (mg) received in all cycles divided by the baseline BSA and the number of treatment cycles for a particular drug.

[c] Relative Dose Intensity is the ratio of dose intensity and planned dose intensity.

Outcomes and estimation

Primary endpoint: Overall Response Rate After 4 Cycles

Results for the primary endpoint are presented in the table below, where confirms non-inferiority of SC compared with IV administration was confirmed. The ORR after 4 cycles in the IV treatment group in Study MMY-3021 was consistent with that observed in historical studies of single-agent VELCADE in multiple myeloma studies (41% in Study M34101-039 [APEX] and 38% in Study MMY-3001). The stratified Mantel-Haenszel estimate of the relative risk of achieving response for SC versus IV was 0.99 (95% CI: 0.71, 1.37), which excludes the pre-specified non-inferiority margin 0.6.

Table 13 – Summary of ORR during first 4 cycles (Study MMY-3021 – Response evaluable analysis set)

	-------- IV -------- - N (%) -	-------- SC -------- - N (%) -
Total no. subjects	73	145
Overall response rate (CR+PR)[a]	31 (42)	61 (42)
Non-inferiority		
95% CI for ORR_SC - .6 ORR_IV		(6.1 , 27.1)
P-value		0.00201

Note: CI and p-value are based on normal approximation.
[a] Based on programmed algorithm
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Secondary Efficacy Endpoints - CR, nCR, and VGPR Rates after 4 cycles and after 8 cycles

Results of the secondary endpoints regarding best response after first 4 cycles or after 8 cycles are presented respectively in the tables below.

Table 14 – Summary of Best Response during first 4 cycles (Study MMY-3021 – Response evaluable analysis set)

Best Response[a]	--- IV --- - N (%) -	--- SC --- - N (%) -	--- Rate Difference -- 95% CI[b]	-- Relative Risk[c] - 95% CI	P-value[d]
Total no. subjects	73	145			
Complete response (CR)	6 (8)	9 (6)	-2.0 (-9.4 , 5.4)		
Partial response (PR)	25 (34)	52 (36)	1.6 (-11.8 , 15.0)		
- near CR	4 (5)	9 (6)	0.7 (-5.8 , 7.3)		
- very good PR	2 (3)	6 (4)	1.4 (-3.6 , 6.4)		
At least very good PR	12 (16)	24 (17)	0.1 (-10.3 , 10.5)		
Overall response rate (CR, PR)	31 (42)	61 (42)	-0.4 (-14.3 , 13.5)	0.99 (0.71,1.37)	0.00201
Minor response (MR)	10 (14)	20 (14)	0.1 (-9.6 , 9.8)		
Overall response + MR	41 (56)	81 (56)	-0.3 (-14.3 , 13.7)	0.99 (0.77,1.26)	0.00004
No change	25 (34)	49 (34)			
Progressive disease	5 (7)	9 (6)			
Not evaluable	2 (3)	6 (4)			

Note: Very Good PR is a subcategory of PR where subjects meet the following criteria:
Heavy chain subjects: At least 90% reduction in serum m-protein and urine m-protein <100 mg/24hr.
Light chain subjects: Non-measurable serum m-protein and urine m-protein <100 mg/24hr.
Note: Near CR is a subcategory of PR where subjects meet the following criteria:
Positive immunofixation analysis of serum or urine as the only evidence of disease.
Disappearance of any soft tissue plasmacytomas.
Note: At Least VGPR includes categories of Very Good PR, Near CR, and Complete Response.
[a] Based on programmed algorithm.
[b] 95% CI for SC rate - IV rate is based on normal approximation
[c] Stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV is used.
[d] P-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in IV.

Table 15 – Summary of Best Response during first 8 cycles (Study MMY-3021 – Response evaluable analysis set)

Best Response[a]	--- IV --- - N (%) -	--- SC --- - N (%) -	--- Rate Difference -- 95% CI[b]	-- Relative Risk[c] - 95% CI	P-value[d]
Total no. subjects	73	145			
Complete response (CR)	9 (12)	15 (10)	-2.0 (-11.0 , 7.0)		
Partial response (PR)	29 (40)	61 (42)	2.3 (-11.5 , 16.1)		
- near CR	7 (10)	14 (10)	0.1 (-8.2 , 8.4)		
- very good PR	2 (3)	7 (5)	2.1 (-3.0 , 7.2)		
At least very good PR	18 (25)	36 (25)	0.2 (-12.0 , 12.3)		
Overall response rate (CR, PR)	38 (52)	76 (52)	0.4 (-13.7 , 14.4)	1.00 (0.77,1.31)	0.00010
Minor response (MR)	11 (15)	14 (10)	-5.4 (-14.9 , 4.1)		
Overall response + MR	49 (67)	90 (62)	-5.1 (-18.4 , 8.3)	0.92 (0.75,1.12)	0.00003
No change	17 (23)	40 (28)			
Progressive disease	5 (7)	9 (6)			
Not evaluable	2 (3)	6 (4)			

Note: VGPR (Very Good PR) is a subcategory of PR where subjects meet the following criteria: Heavy chain subjects: At least 90% reduction in serum M-protein and urine M-protein <100 mg/24hr. Light chain subjects: Non-measurable serum M-protein and urine M-protein <100 mg/24hr.
Note: Near CR is a subcategory of PR where subjects meet the following criteria: Positive immunofixation analysis of serum or urine as the only evidence of disease. Disappearance of any soft tissue plasmacytomas.
Note: At Least VGPR includes categories of Very Good PR, Near CR, and Complete Response.
[a] Based on programmed algorithm.
[b] 95% CI for SC rate - IV rate is based on normal approximation
[c] Stratified Mantel-Haenszel estimate of the common relative risk of SC vs IV is used.
[d] P-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in IV.

Secondary Efficacy Endpoints - Time to Disease Progression

Table 16 presents a summary of time to disease progression (censored for subsequent therapy) for the ITT population in Study MMY-3021. These results indicate that TTP (censored for subsequent therapy), was similar in the SC and IV treatment groups.

Table 16 – Summary of Time to Disease Progression (censored for subsequent therapy) (Study MMY-3021 – Intent-to Treat analysis set)

Descriptive[a]	IV (N=74)	SC (N=148)	Total (N=222)
Time to Disease Progression (days)			
Number of Assessed	74	148	222
Number of Censored (%)	33 (44.6)	84 (56.8)	117 (52.7)
Number of Events (%)	41 (55.4)	64 (43.2)	105 (47.3)
25% Quantile (95% CI)	156.0(116.0; 210.0)	151.0(113.0; 227.0)	151.0(128.0; 205.0)
Median (95% CI)	287.0(231.0; 323.0)	316.0(259.0; 357.0)	298.0(259.0; 320.0)
75% Quantile (95% CI)	369.0(302.0; NE)	527.0(358.0; NE)	434.0(358.0; NE)
P-value[b]	0.38657		
Hazard Ratio (95% CI)[c]		0.839 (0.564;1.249)	

NE=Not estimable.
[a] Based on Kaplan-Meier product limit estimates.
[b] Log rank test adjusted for stratification factors: ISS staging and Number of prior lines.
[c] Hazards ratio estimate is based on a Cox's model adjusted for stratification factors: ISS staging and Number of prior lines.

Figure 6 presents a Kaplan-Meier plot of time to disease progression (censored for subsequent therapy for the ITT population in Study MMY-3021.

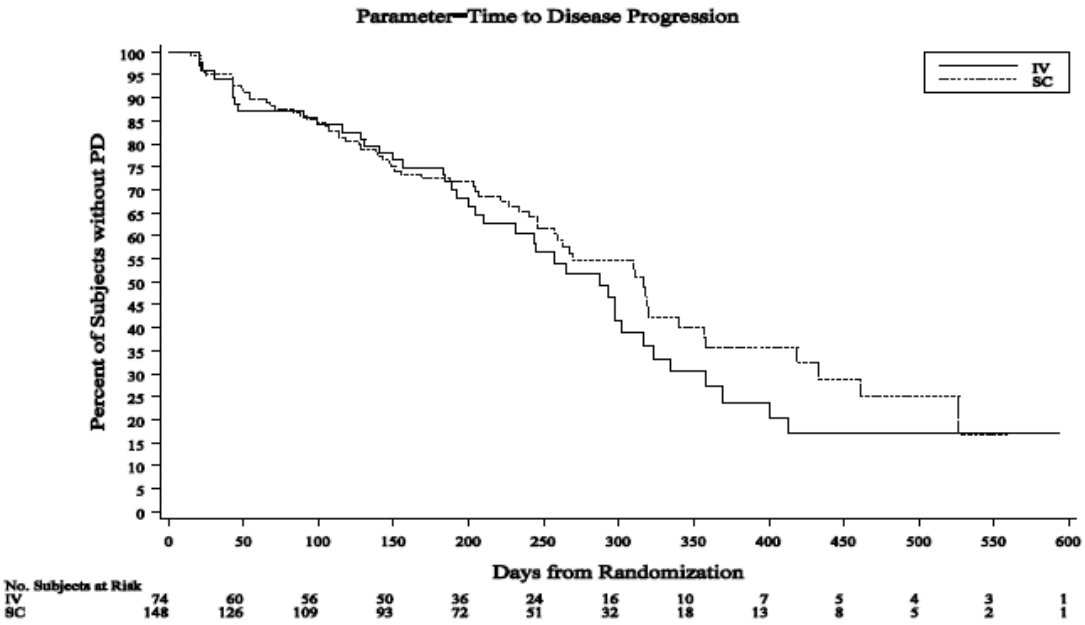

Figure 6 – Kaplan-Meier Plot of Time to Disease Progression (censored for subsequent therapy) (Study MMY-3021 – Intent-to Treat analysis set)

Secondary Efficacy Endpoints - Progression-Free Survival

A total of 130 PFS events were observed (82 events [55.4% of subjects] in the SC treatment group and 48 events [64.9% of subjects] in the IV treatment group). The median PFS was 310 days (10.2 months) in the SC treatment group and 245 days (8.0 months) in the IV treatment group. Ninety-two (41.4%) of all subjects were censored. The hazard ratio (SC vs. IV) was 0.824 (95% CI: 0.574, 1.183), and the p-value was 0.29450 (stratified log-rank test). These results indicate that PFS (censored for subsequent therapy) is similar in the SC and IV treatment groups. The percentage of total patients censored was 40.1%; in the SC group the percentage was 43.2 and in the IV group was 33.8.

Secondary Efficacy Endpoints - One-Year Survival

A total of 59 deaths were observed (41 in the SC treatment group [27.7% of subjects] and 18 in the IV treatment group [24.3% of subjects]). After a median follow-up of 11.8 months, survival data were not yet mature (27% of events observed). As of the clinical cut-off date of 31 Aug 2010, median survival was 654 days (21.5 months) in the IV treatment group, and not yet reached in the SC treatment group.

The median estimates were not considered reliable, as the Kaplan-Meier curves either did not cross or barely crossed the median (50%) line close to the maximum follow-up, at which point very few subjects remained at risk for death. The 1-year survival rate was 72.6% (95% CI: 63.1, 80.0) for the SC treatment group and 76.7% (95% CI: 64.1, 85.4) for the IV treatment group. The p-value for testing the difference in 1-year survival rate was 0.50368, which indicates that there is no difference in 1-year survival rate between the SC and the IV treatment groups.

Table 17 – Summary of Overall Survival (Study MMY-3021 – Intent-to Treat analysis set)

Descriptive[a]	IV (N=74)	SC (N=148)	Total (N=222)
Overall survival (days)			
Number of Assessed	74	148	222
Number of Censored (%)	56 (75.7)	107 (72.3)	163 (73.4)
Number of Events (%)	18 (24.3)	41 (27.7)	59 (26.6)
25% Quantile (95% CI)	417.0(231.0; NE)	355.0(250.0; 472.0)	355.0(258.0; 472.0)
Median (95% CI)	654.0(532.0; NE)	NE (520.0; NE)	654.0(532.0; NE)
75% Quantile (95% CI)	NE (654.0; NE)	NE (NE ; NE)	NE (NE ; NE)
1 Yr Survival Rate % (95% CI)	76.7(64.1; 85.4)	72.6(63.1; 80.0)	73.9(66.6; 79.9)
P-value[b]	0.50368		

NE=Not estimable.

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

[b] P-value is for the hypothesis that there is no difference in 1-year survival rate between the SC and IV arms.

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The percentage of total patients censored was 73.4% (72.3% in the SC group and 75.7% in the IV group).

Secondary Efficacy Endpoints – Time to Response

Based on the Kaplan-Meier estimates, the median time to first response was 3.5 months in both the SC treatment group (106 days) and the IV treatment group (108 days). The hazard ratio (SC vs. IV) was 1.059 (95% CI: 0.716, 1.567), and the p-value was 0.77247 (stratified log-rank test), indicating that the time to first response was similar between the SC and IV treatment groups

For responders, the median time to first response was 1.4 months in both the SC treatment group (44 days) and the IV treatment group (43 days).

The median time to best response was 106 days (3.5 months) in the SC treatment group and 128 days (4.2 months) in the IV treatment group. The hazard ratio (SC vs. IV) was 1.049 (95% CI: 0.710, 1.552), and the p-value was 0.80777 (stratified log-rank test), indicating that the time to best response was similar between the SC and IV treatment groups.

For responders, the median time to best response was 49.5 days (1.6 months) in the SC treatment group and 46 days (1.5 months) in the IV treatment group.

The median time to CR was not estimable for both the SC and IV treatment groups, because only 12% of subjects had best response CR. The hazard ratio (SC vs. IV) was 1.026 (95% CI: 0.456, 2.308), and the p-value was 0.95127 (stratified log-rank test), indicating that the time to CR was similar between the SC and IV treatment groups.

For responders, the median time to CR was 87 days (2.9 months) for the SC treatment group and 44 days (1.4 months) for the IV treatment group; however, this difference should be interpreted with caution because of the relatively small number of subjects with CR.

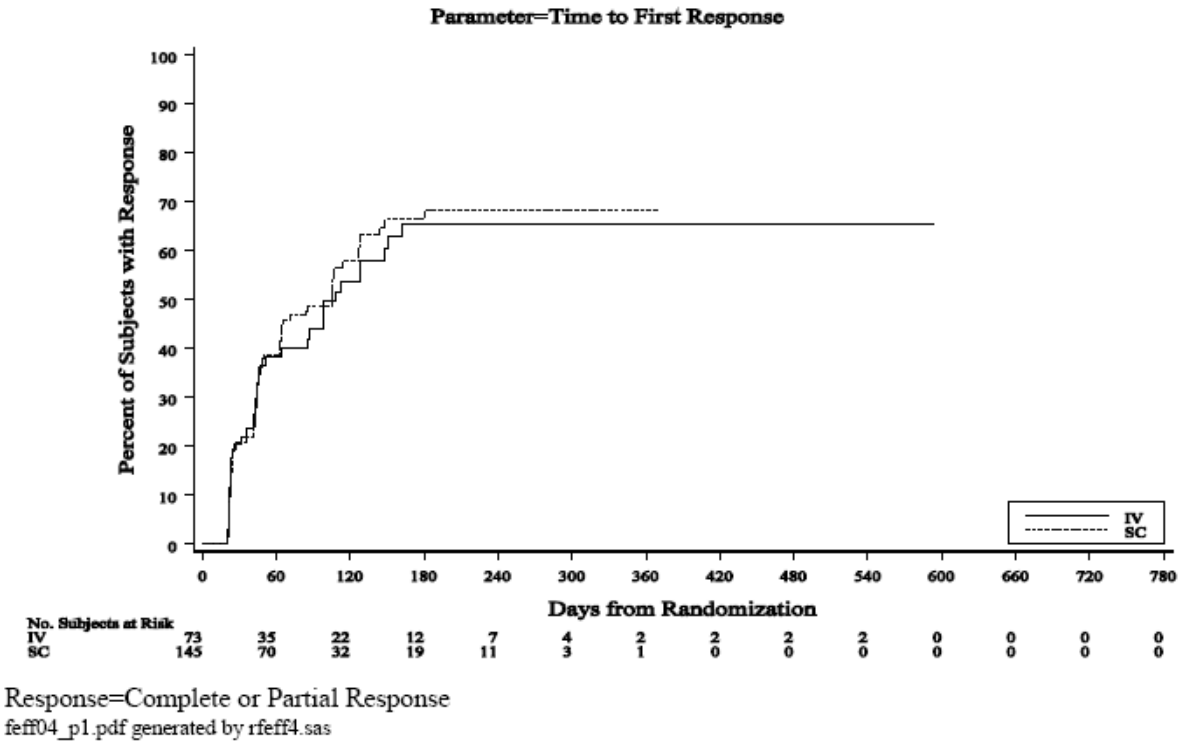

Figure 7 – Kaplan-Meier Plot of Time to First Response (Study MMY-3021 – Response evaluable analysis set)

Ancillary analyses

A number of Exploratory Analyses of the primary and secondary endpoints (e.g. adjusted for baseline covariates, censored for subsequent therapy) were performed. These results indicate that the endpoint results were comparable between the SC and IV treatment groups.

Summary of main study

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 18 – Summary of Efficacy for trial MMY-3021

Title: An Open-Label, Randomized Study of Subcutaneous and Intravenous VELCADE® in Subjects With Previously Treated Multiple Myeloma		
Study identifier	EudraCT Number: 2008-000952-28	
Design	This was a randomized, open-label, international, multicenter, phase 3 study that evaluated VELCADE in subjects with multiple myeloma who had received 1 to 3 prior lines of therapy and had measurable evidence of disease progression since their last previous therapy. Subjects were randomly assigned in a 2:1 ratio to receive 1.3 mg/m2 VELCADE either SC or IV. The planned total sample size was approximately 216 subjects.	
	Duration of main phase:	24-week open-label treatment phase (maximum of 30 weeks for subjects who received an additional 2 cycles of treatment after Sponsor approval)
	Duration of Run-in phase:	21 days

	Duration of Extension phase:	1 year after the last subject was randomized	
Hypothesis	Noninferiority: The noninferiority of SC treatment compared to IV treatment was tested. Noninferiority was defined as retaining 60% of the IV (active control) treatment effect as measured by ORR. The hypothesis used was: H0: ORRSC – 0.60 ORRIV < 0 versus H1: ORRSC – 0.60 ORRIV ≥0 (noninferiority)		
Treatment groups	SC		VELCADE 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 3-week cycle for 8 cycles. response-evaluable n=145, safety evaluable n=147
	IV		VELCADE 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 3-week cycle for 8 cycles. response-evaluable n= 73, safety evaluable n=74
Endpoints and definitions	Primary composite endpoint	ORR	ORR (CR + PR) rate after 4 cycles of VELCADE Noninferiority
	Secondary endpoints (pivotal ones)		CR, nCR, and VGPR Rates After 4 Cycles Response Rate After 8 cycles Time to Progression Progression Free Survival One Year Survival
	Other efficacy criteria		Best M-Protein Response
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Results and Analysis

Analysis description	Primary Analysis			
Analysis population and time point description	**Response evaluable population**			
Descriptive statistics and estimate variability	Treatment group	SC	IV	
	Number of subjects	145	73	
	ORR	42%	42%	
	Non-inferiority	p=0.00201		95% CI for ORR_SC - .6 ORR_IV
	CR, nCR, VGPR after 4 cycles	17% at least VGPR	16% at least VGPR	

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

An exploratory analysis of pooled efficacy data from Studies MMY-3021 and CAN-1004 was undertaken to provide a comprehensive assessment of all available efficacy data for the SC route of VELCADE administration.

Most demographic characteristics were similar between the pooled SC and IV treatment groups. The median age was 64.0 years in both the SC and IV treatment groups (range: 38 to 88), with 52% of all subjects <65 years of age. The SC treatment group had 51% male subjects, whereas the IV treatment group had 58% male subjects. No noteworthy differences were observed in the number of treatment cycles received by subjects in the SC and IV treatment groups, and the median VELCADE dose intensity was 4.84 mg/m2 per cycle in the SC treatment group and 4.78 mg/m2 per cycle in the IV treatment group. A similar percentage of subjects in the SC treatment group (53%) and the IV treatment group (50%) received dexamethasone.

For the integrated efficacy data from response-evaluable subjects in Studies MMY-3021 and CAN-1004, the ORR was 53% in the SC treatment group and 51% in the IV treatment group. The stratified Mantel-Haenszel estimate of the relative risk of achieving response (CR or PR) for SC versus IV was 1.04 (95% CI: 0.81, 1.35). Response rates were similar between the integrated SC and IV treatment groups across all subpopulations analyzed (age, sex, and number of lines of prior therapy).

Supportive study CAN-1004

The phase 1 pilot study CAN-1004 (n=24) was not powered to assess efficacy endpoints. However, the results of analyses of efficacy data from Study CAN-1004 suggesting that the SC and IV routes were similar with regard to the effect of treatment on disease response was confirmed by the statistically significant finding of non-inferiority observed in Study MMY 3021.

For TTP, after a median follow up of 6.6 months, a total of 6 events were observed (2 [17%] SC vs. 4 [33%] subjects IV). The median TTP (Kaplan-Meier estimate) was not estimable for the SC treatment group and was 7.4 months for the IV treatment group. The hazard ratio was 0.804 (95% CI: 0.134, 4.826) favouring the SC treatment group.

The 6 month PFS rate was 76.4% in the SC treatment group and 75.8% in the IV treatment group. After a median follow-up of 6.6 months, no deaths were reported in either treatment group.

Therefore, the results of Study CAN-1004 were consistent with those from Study MMY 3021, and differences in efficacy were likely related to smaller sample size and the limited scope of efficacy analyses performed in the pilot study. Data on long-term efficacy endpoints were not available for Study CAN-1004; however the 6 month PFS rate in that study was consistent with that later observed in Study MMY 3021 (68.9% SC vs. 70.8% IV).

1.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The study was performed in subjects with progressive multiple myeloma, consistently with the target population for which Velcade is already approved. Based on the results of the pilot phase 1 study CAN-1004, Velcade was administered at its approved dose and schedule, and the same dose was used in both arms (IV and SC routes of administration).

The choice of Response Rate (RR) as the primary efficacy endpoint is considered appropriate and is enforced by secondary endpoints and exploratory efficacy analysis.

Tumour assessment was performed at planned time-points and was symmetrical in the two treatment arms. M-protein assessment was centralised and blinded, although bone marrow samples and radiology assessment of skeletal or extramedullary plasmacytomas, were not independently centrally reviewed.

Baseline demographic characteristics were well-balanced between the two treatment groups except for gender and world region that showed both inter and intra groups differences. However, results from subgroup analysis of ORR after 4 cycles and TTP by Sex and Region indicated a limited and non significant impact of gender and world regions.

In Study MMY-3021, baseline disease characteristics were well balanced although slight differences can be observed between the two groups for some factors with prognostic relevance.

In the SC arm there was a slight prevalence of patients with impaired renal function, lytic bone lesions and poorer Karnofsky Performance Status (KPS): patients with KPS < 80 were 61% in the SC group and 48% in the IV group. In the IV group there were more patients with high risk cytogenetic abnormality. The MAH clarified that subjects were stratified by the number of lines of prior therapy (1 vs. >1) and International Staging System (Stages I, II, and III). With the targeted 216 subjects (222 actually randomized), there was no possibility to add a third stratification parameter.

The observed imbalances were all in favour of the IV treatment group, with the exception of high-risk cytogenetic abnormalities which was in favour of the SC group.

The ORR during the first 4 cycles together with the stratified Mantel-Haenszel estimate of the common relative risk of achieving response for SC versus IV, was evaluated for a number of subgroups including the cytogenetic abnormalities (high-risk, standard risk, and not done) subgroup. The point estimate of the relative risk in the high-risk cytogenetic subgroup (and all other subgroups) was cantered around 1, and in none of the subgroups did the 95% CI exclude 1. This indicates that the impact of high-risk cytogenetics on the primary endpoint was limited. Overall, these results confirm the consistency of VELCADE activity regardless of baseline characteristics.

With regard to prior therapy, it should be noted that although treatment groups were well balanced for the number of previous lines of therapy, patients in the IV arm had received more frequently High Dose Stem Cell Transplant (27% vs 21%), anthracyclines (43% vs 39%), alkylating agents (88% vs 86%), thalidomide (46% vs 39%), lenalidomide (12% vs 8%) and IMID (53% vs 42%).

However, the subgroup analyses for ORR after the first 4 cycles, performed to evaluate the impact of these imbalances in the treatment groups, did not show any relevant differences.

In both treatment groups, the rate of patients who completed the planned cycles of treatment and discontinued due to disease progression, was the same. Moreover, reasons for discontinuation other than disease progression (adverse events, death during treatment), were equally represented in the SC and IV treatment groups.

Efficacy data and additional analyses

Efficacy results were comparable between SC and IV treatment groups.

The same European Group for Blood and Marrow Transplantation (EBMT) response criteria and validated computer-programmed statistical analysis software algorithm, as in previous trials were used.

The study met the non-inferiority objective with an ORR of 42%, after 4 cycles, in both arms: these results are in line with historical data with single-agent Velcade. Results in the response-evaluable population were confirmed in a sensitivity analysis in the ITT population.

ORR after 8 cycles was 52% in both arms. The addition of dexamethasone improved response to a similar degree in both arms: 30% of subjects with no response at the end of cycle 4 obtained a PR at the end of cycle 8, and 13 % with PR at cycle 4 obtained a CR at cycle 8.

For the integrated efficacy data from response-evaluable subjects in Studies MMY 3021 and CAN-1004 (pooled analysis), the ORR was 53% in the SC treatment group and 51% in the IV treatment group. The stratified Mantel-Haenszel estimate of the relative risk of achieving response (CR or PR) for SC versus IV was 1.04 (95% CI: 0.81, 1.35).

The non-inferiority of the SC formulation compared to the IV formulation, was demonstrated based on the choice of a non-inferiority margin of 60%. Indeed, the 60% retention chosen by the MAH is rather arbitrary and is potentially wide (CI 6.1, 27.1). It is noted that, although the observed difference in ORR was relatively small (-0.4%), the inferior CI margin for the non inferiority of SC vs IV is close to the 60% retention margin potentially leaving uncertainties on the estimated efficacy. However, given the context of this particular non inferiority setting in which the same active substance is given by different routes of administration and PK data have confirmed similar overall exposure between IV and SC use, a non-inferiority margin can actually be used to assess the "precision" of the estimate of treatment effect rather than the clinical relevance. In this scenario, the point estimates, ORR both 42% for IV and SC use, can be considered reassuring as opposed to the formal conclusion of the non inferiority exercise that the width of the resulting CI leaves too much uncertainty about the estimated efficacy.

MMY-3021 study results continued to support the additional efficacy benefit observed following administration of dexamethasone to treatment regimen after 4 cycles, this observation needs to be reflected in the SmPC section 5.1 (addition of dexamethasone in patients with documented suboptimal response (no change + PR).

The potential benefit of an earlier introduction of dexamethasone therapy could not be definitely established, considering that a late response to bortezomib (and not a response to the combination with dexamethasone), could not be excluded in the absence of a control group.

ORR rate is only accepted as primary endpoint when the results are supported by the results of the secondary endpoint PFS and 1 year survival. The updated analysis, provided at the median follow up of 17.5 months (data cut off on February 26th 2011), confirms the initial PFS result (improvement of 0.9 month in favour of SC treatment) and shows a smaller difference in 1-year survival rate between SC and IV regimen (1.6% compared to 4.1% in the original analysis) with a median survival not yet reached in the IV treatment group.

However, based on the immaturity of survival data (32% of death events observed) and the rate (27.5%) of patients censored for progression events, efficacy results of Study MMY-3021 cannot be seen as final. Results from 1-year OS and PFS provided with the update are consistent with the primary efficacy endpoint of the pivotal trial MMY-3021, ORR observed after 4 cycles.

Results for secondary endpoints were similar in both arms, although the high rate of censored patients TTP (53%), PFS (40%), 1-year survival rate (73%), should be considered.

The MAH clarified that the imbalance in the number of censored patients for PFS and time to progression (TTP) between the IV and SC groups was due to the lower percentage of events (disease progression for TTP, disease progression or death for PFS) in the SC arm. This observation is also substantiated by the hazard ratios: for TTP, the hazard ratio (SC vs. IV) was 0.839 with 95% CI (0.564, 1.249); for PFS, the hazard ratio (SC vs. IV) was 0.824 with 95% CI (0.574, 1.183). Both of them are in favour of the SC arm. The 1-year survival rate was 73% in the SC arm, which was numerically lower than what was observed in the IV arm (77%). However, the p-value is 0.5037 for testing the difference in 1-year survival rate between the SC and IV arm. This demonstrates that the 1-year survival rates were similar between SC and IV arm.

Information was provided on time and reason of censoring for disease progression, PFS and OS. In all the three Kaplan-Meier plot the number of censored was higher in the initial part of the curve in both arms. Moreover, the rate of censored by reason for censoring seems to be balanced between the two arms.

1.5.4. Conclusions on the clinical efficacy

Velcade given subcutaneously was non-inferior in terms of efficacy (ORR after 4 cycles = 42% for IV and SC analysis) compared to IV administration. The ORR was 52% in both the SC and IV treatment groups after 8 cycles. This result is in line with overall PK/PD findings.

The stratified Mantel-Haenszel estimate of the relative risk of achieving response for SC versus IV was 0.99 with 95% CI (0.71, 1.37), which excludes the pre-specified non-inferiority margin 0.6.

1.6. Clinical safety

Patient exposure

The safety data was reviewed from Study CAN-1004 (N=24 [12 IV + 12 SC]) and Study MMY-3021 (N=221 [74 IV + 147 SC]).

Supportive safety data were from pooled analysis for the VELCADE SC and IV administration:

- Pooled data from the 2 subcutaneous studies of VELCADE, Study MMY-3021 and Study CAN-1004. The primary objective of the pooled safety data analyses was to compare the observed safety pattern of VELCADE administered SC to VELCADE administered IV in subjects with previously treated multiple myeloma in Studies MMY-3021 and CAN-1004.

- Integrated data from 8 historical studies (M34100-024, M34100-025, M34101-029, M34101-039 [VELCADE treatment group], M34101-040, DOXIL-MMY-3001 [VELCADE control group], JPN-MM-101/201, and JPN-MM-301). Integrated safety data in 1356 subjects who received IV VELCADE administered at a starting dose of 1.3 mg/m2, with or without the addition of dexamethasone, in 8 completed sponsor-initiated studies are also included as a reference.

Within the pooled safety population from the two studies, 245 subjects were treated with at least 1 dose of VELCADE: 86 subjects by the IV route and 159 subjects by the SC route. The difference in size of the 2 groups was due to the 2:1 randomization ratio used in Study MMY-3021 to increase the statistical power of efficacy endpoints.

The median number of VELCADE cycles administered was the same for both treatment groups at 8 cycles (range; 1-10 for both groups). In the SC and IV treatment groups, 79% and 77% of subjects, respectively, received at least 4 cycles of treatment. After Cycle 4, some asymmetry was observed between the treatment groups with more subjects on treatment in the SC treatment group; the percentage of subjects receiving 5 cycles in the SC and IV treatment groups was 70% vs. 66%, respectively, and the percentage of subjects receiving 8 cycles was 56% and 51%, respectively.

Dexamethasone was added to the treatment regimen for 53% of subjects in the SC treatment group and 50% of subjects in the IV treatment group.

The median duration of VELCADE treatment was the same for both the SC and IV treatment groups at 22.57 weeks and 22.29 weeks (7.6 cycles), respectively.

Adverse events

The table below summarises the adverse events reported in the two studies.

Table 19 – Comparison of Safety Characteristics for the Supportive VELCADE Studies MMY-3021 and CAN-1004

	MMY-3021 (N=221) IV/SC n (%)	CAN-1004 (N=24) IV/SC n (%)
Any adverse event	73 (99) / 140 (95)	12 (100) / 11 (92)
Related adverse event	67 (91) / 124 (84)	12 (100) / 11 (92)
Any serious adverse event	26 (35) / 53 (36)	5 (42) / 1 (8)
Related serious adverse event	14 (19) / 29 (20)	2 (17) / 1 (8)
≥ Grade 3 toxicity adverse event	52 (70) / 84 (57)	9 (75) / 7 (58)
Related Grade ≥3 toxicity adverse event	41 (55) / 58 (39)	8 (67) / 6 (50)
Adverse events causing d/c study drug	20 (27) / 33 (22)	6 (50) / 2 (17)
Related adverse events causing d/c study drug	17 (23) / 26 (18)	4 (33) / 2 (17)
Deaths due to at least 1 related adverse event	2 (3) / 2 (1)	0 / 0

d/c = discontinuation

Data from the IV treatment group in the 2 pooled randomized SC studies were compared with the integrated historical IV studies. Grade ≥3 adverse events and VELCADE discontinuations due to adverse events were consistent between the pooled IV treatment group in the randomized SC studies and the integrated historical IV studies (Table 20).

Table 20 – Overview of Treatment-Emergent Adverse Events for MMY-3021, Pooled Data and Historical Studies

	---------- MMY3021 -------		-- MMY3021 + CAN1004 --		Historical
	IV (N=74) n (%)	SC (N=147) n (%)	IV (N=86) n (%)	SC (N=159) n (%)	VELCADE IV (N=1356) n (%)
Any TEAE	73 (99)	140 (95)	85 (99)	151 (95)	1345 (99)
At least one related	67 (91)	124 (84)	79 (92)	135 (85)	1286 (95)
At least one VELCADE-related	67 (91)	124 (84)	79 (92)	135 (85)	1286 (95)
Any serious TEAE	26 (35)	53 (36)	31 (36)	54 (34)	647 (48)
Maximum severity of any TEAE	73 (99)	140 (95)	85 (99)	151 (95)	1345 (99)
Grade 1	3 (4)	4 (3)	3 (3)	4 (3)	32 (2)
Grade 2	18 (24)	52 (35)	21 (24)	56 (35)	247 (18)
Grade 3	35 (47)	54 (37)	43 (50)	61 (38)	766 (56)
Grade ≥4	17 (23)	30 (20)	18 (21)	30 (19)	300 (22)
Grade ≥3	52 (70)	84 (57)	61 (71)	91 (57)	1066 (79)
Terminated treatment due to TEAEs	20 (27)	33 (22)	26 (30)	35 (22)	458 (34)
At least one related	17 (23)	26 (18)	21 (24)	28 (18)	311 (23)
At least one VELCADE-related	17 (23)	25 (17)	21 (24)	27 (17)	310 (23)

TEAE=treatment-emergent adverse event
Note: Percentages calculated with the number of subjects in each group as denominator.
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Table 21 summarizes the incidence of the most frequent (at least 10% in either treatment group) treatment-emergent adverse events by MedDRA SOC for the integrated historical IV studies.

Table 21 – Incidence of Most Frequent (at Least 10% in Any Treatment Group) Adverse Events by MedDRA SOC (MMY-3021, CAN-1004, and Historical VELCADE IV)

System Organ Class	- MMY3021 + CAN1004 - IV (N=86) n (%)	SC (N=159) n (%)	Historical VELCADE IV (N=1356) n (%)
Total no. subjects with TEAE	85 (99)	151 (95)	1345 (99)
Blood and lymphatic system disorders	49 (57)	95 (60)	779 (57)
Cardiac disorders	9 (10)	18 (11)	211 (16)
Eye disorders	12 (14)	16 (10)	270 (20)
Gastrointestinal disorders	52 (60)	63 (40)	1142 (84)
General disorders and administration site conditions	53 (62)	86 (54)	1063 (78)
Hepatobiliary disorders	7 (8)	16 (10)	29 (2)
Infections and infestations	47 (55)	78 (49)	871 (64)
Injury, poisoning and procedural complications	2 (2)	6 (4)	195 (14)
Investigations	4 (5)	26 (16)	344 (25)
Metabolism and nutrition disorders	23 (27)	42 (26)	651 (48)
Musculoskeletal and connective tissue disorders	37 (43)	51 (32)	800 (59)
Nervous system disorders	60 (70)	92 (58)	1002 (74)
Psychiatric disorders	12 (14)	23 (14)	484 (36)
Renal and urinary disorders	7 (8)	22 (14)	243 (18)
Respiratory, thoracic and mediastinal disorders	29 (34)	37 (23)	692 (51)
Skin and subcutaneous tissue disorders	16 (19)	38 (24)	598 (44)
Vascular disorders	15 (17)	29 (18)	333 (25)

TEAE=treatment emergent adverse event; no.=number
Note: Percentages calculated with the number of subjects in each group as denominator.
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The principal SOC reporting more than 10% higher incidence rates in the SC group than in the IV one, was investigations. This difference is due to a 14% incidence of the adverse event of 'weight decreased' in the SC treatment group as compared with 2% for the IV treatment group. The incidence of weight decrease was mild to moderate in severity. Grade 1 weight decrease was reported for 9% of subjects in the SC group compared with 1% in the IV group; Grade 2 was reported for 5% and 0%, respectively. In the IV group, 1% of subjects had Grade 3 weight decrease, and no Grade 3 weight decrease was reported for the SC treatment group. An analysis of the collected weight data only showed a difference in incidence of Grade 1 weight loss.

A comparison of adverse events by preferred term for SC and IV treatment groups showed a ≥10% difference between the 2 groups in the incidence of diarrhoea (25% vs. 40%) and peripheral sensory neuropathy (33% SC vs. 44% IV), in favour of the SC treatment group.

Of the 159 subjects who received at least 1 SC injection, 96 (60%) subjects reported at least 1 local SC injection site reaction during the study, with 89 (56%) subjects already having a reaction in the first cycle. Out of the 615 injections administered during Cycle 1, 239 (39%) injections were associated with redness. Reactions of redness appeared to diminish over the course of the cycle, with 47% of subjects having a reaction at Cycle 1, Day 1 and 34% of subjects having a reaction at Cycle 1, Day 11.

A number of subgroup analyses were performed. Overall, the majority of subjects in each subgroup experienced at least 1 adverse event, with incidences comparable across all subgroups (range, 92% - 100%).

Serious adverse event/deaths/other significant events

Serious adverse events

The overall incidence of serious adverse events was similar for the SC treatment group (34%) compared with the IV treatment group (36%). Furthermore, the incidence of serious adverse events by SOC was very similar between the 2 treatment groups with a <5% difference noted for most SOCs.

The only exception occurred in the General Disorders and Administration Site Conditions SOC where subjects in the SC treatment group had a 7% incidence of serious adverse events compared with 1% for the IV treatment group.

Incidence rates for all individual serious adverse events were also low (<5%), except for the percentage of subjects with pneumonia, which was the same for both groups (6%).

There was a difference of ≥10% for the Investigations SOC in favour of the IV treatment group (16% vs. 5%). This difference was primarily due to a 14% incidence of the preferred term "weight decreased" in SC treatment group compared with 2% for the IV treatment group. In an analysis of body weight data there was only a 5% difference between groups for Grade 1 weight decrease (5% to <10% change in body weight) in the SC treatment group (21% SC vs. 16% IV) and no difference in higher grade weight change.

A comparison of the SC and IV treatment groups of pooled safety data from studies MMY-3021 and CAN-1004 showed that 57% of subjects in the SC treatment group and 71% of subjects in the IV treatment groups had Grade ≥3 adverse events. Differences between the SC and IV treatment groups of ≥5% were observed in Musculoskeletal and Connective Tissue Disorders (1% vs. 9%), Nervous System Disorders (14% vs. 23%), and Respiratory, Thoracic and Mediastinal Disorders (4% vs. 10%).

Grade ≥3 adverse events by SOC with the highest frequency were: Blood and Lymphatic System Disorders (33% SC and 37% IV), and most commonly included neutropenia (18% SC vs. 22% IV) and thrombocytopenia (14% SC vs. 20% IV); Nervous System Disorders (14% vs. 23%), specifically peripheral sensory neuropathy (4% SC vs. 14% IV) and neuralgia (3% SC vs. 8% IV).

Deaths

The table below summarizes all causes of mortality occurring within 30 days after the last dose of study medication; for Study MMY-3021, study medication was either VELCADE or VELCADE in combination with dexamethasone.

Table 22 – Summary of All-Cause Mortality Within 30 Days After Last Dose (MMY-3021, CAN-1004, and Historical VELCADE IV)

	---- MMY3021 + CAN1004 ----		---- Historical ---
	IV (N=86)	SC (N=159)	VELCADE IV (N=1356)
	n (%)	n (%)	n (%)
Deaths within 30 days after last dose[a]	5 (6%)	8 (5%)	113 (8%)
95% confidence interval[b]	1.915 - 13.619	2.197 - 9.919	6.917 - 9.940
Treatment-related deaths within 30 days after last dose[c]	1 (1%)	2 (1%)	17 (1%)
95% confidence interval[b]	0.029 - 8.148	0.153 - 5.125	0.732 - 2.021
VELCADE-related deaths within 30 days after last dose[d]	1 (1%)	2 (1%)	17 (1%)
95% confidence interval[b]	0.029 - 8.148	0.153 - 5.125	0.732 - 2.021

[a] Per protocol, 28 days for studies JPN-MM-101/201/301 and 20 days for studies M34100-024/025
[b] Confidence intervals were based on F-approximation for unadjusted incidence rates.
[c] Includes all deaths due to adverse events that were related to one of the two study drugs: VELCADE, or dexamethasone.
[d] Includes those deaths due to adverse events that were related to VELCADE.

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One sudden death (under General disorders and administration site conditions) was recorded in SC pooled population. A higher % of progression disease as cause of death was observed in the SC group (18% SC vs. 9% IV).

Laboratory findings

The majority of subjects in the SC and IV treatment groups experienced Grade 1 or Grade 2 haemoglobin during treatment. Subjects in the SC treatment group had a higher incidence of Grade 2 haemoglobin (50% vs. 41%).

The incidence of Grade ≥3 haematology parameters was lower for subjects in the SC group compared with the IV group, with the exception of Grade ≥3 haemoglobin, which was similar for both treatment groups (14% and 11%). There was an 11% lower incidence of Grade ≥3 neutropenia (22% vs. 33%), a 10% lower incidence of leucopenia (9% vs. 19%), and 4% lower incidence of thrombocytopenia (18% vs. 22%), all in favour of the SC treatment group.

Discontinuation due to adverse events

The rate of discontinuation due to adverse events was 22% (33 subjects) in the SC treatment group compared with 27% (20 subjects) in the IV treatment group.

In both treatment groups, the most frequent adverse events leading to discontinuation occurred in the Nervous System Disorder SOC (12% in the SC treatment group vs 16% in the IV treatment group). Peripheral sensory neuropathy events were the more represented discontinuation-leading adverse events (5% in the SC treatment group vs 12% in the IV treatment group), followed by neuralgia (4% SC vs. 8% IV). The incidence of all other adverse events leading to VELCADE discontinuation was low (<5%).

1.6.1. Discussion on clinical safety

Primary data demonstrating the safety of SC VELCADE administration were provided by Study MMY-3021, with additional data provided by the Phase 1 pilot study CAN-1004.

Although meaningful comparison of the safety profiles from the individual studies is limited by the small number of subjects in the safety population (159 patients), no inconsistency or major concerns, were identified. Therefore, data from Studies MMY-3021 and CAN-1004 were pooled to provide the most possible robust safety characterization of SC VELCADE. In addition, to determine whether the safety findings observed for Studies MMY-3021 and CAN-1004 were consistent with historical findings, an integrated analysis was conducted of safety data from 1,356 subjects enrolled in 8 earlier, completed, sponsor-initiated studies of subjects with previously treated, relapsed multiple myeloma.

Overall, SC route provides improved systemic safety profile with an acceptable local tolerability. The majority of local injection site reactions were redness, of mild or moderate intensity, and resolved in all cases.

The rate of discontinuation due to adverse events was 22% in the SC treatment group compared with 27% in the IV treatment group.

Systemic safety profile favours the SC treatment group with a lower incidence of Grade ≥3 AE and treatment modification. In particular, there was a lower incidence of diarrhoea (25% SC vs. 40% IV) and a lower incidence of peripheral neuropathy Grade ≥2 in the SC group; treatment discontinuation

due to peripheral neuropathy was also inferior in this group than in the IV group (5% vs 12%, respectively).

One of main safety result of study was a lower incidence of peripheral neuropathy between the two treatment groups (38% SC vs. 53% IV). Sensory neuropathy at baseline (Grade 1) was reported by 21% and 27% of subjects in the SC and IV treatment groups, respectively. In prior studies, presence of baseline Grade 1 peripheral neuropathy was identified as the strongest risk factor for worsening neuropathy during bortezomib treatments. According to data submitted, the incidence of Grade ≥2 or Grade ≥3 events was higher despite of baseline sensory neuropathy (yes/no) in the IV group compared to the SC group. The observed reduced risk in peripheral neuropathy associated with the SC route was maintained after adjustment for cumulative dose and for region and was also apparent in patients with pre-existing neuropathy.

Neurotoxicity is a problematic issue with almost all effective drugs available for patients and peripheral sensory neuropathy has been the main reason for dose modification or treatment discontinuation in the current clinical practise. The incidence of peripheral neuropathy with IV administered bortezomib was lower in the historical IV studies than in study MMY-3021: all grade peripheral neuropathy events (56% IV vs. 37% historical IV), Grade ≥2 events (42% IV vs. 27% historical IV), Grade ≥3 events (16% IV vs. 10% historical IV). A possible explanation might be the lower cumulative dose and shorter treatment duration in the earlier studies. However, it is evident that the incidence of peripheral neuropathy when analyzed for the same cumulative dose is lower in the SC treatment group than in the IV treatment group in the randomized SC studies and in the IV historical studies.

Despite the apparent similar tolerability, the incidence of death was slightly higher in the SC group (27%) in comparison to the IV group (24%). Deaths from "Progressive disease" in study MMY-3021 were twice as common in the SC Velcade group versus the IV Velcade group (18% vs. 9% respectively). This may partially be explained by the fact that the mean baseline KPS score was 90 in the IV treatment arm compared with 80 in the SC arm, reflecting poorer overall health in subjects in the SC arm at baseline. Another reason can lay in the imbalance in patients coming from Eastern Europe (66% in SC arm). In fact, the majority of the patients who died during this study were from Ukraine: 3/10 from the IV group and 16/30 (52%) from the SC group; patients from Ukraine were 31% of all subjects enrolled from Eastern European countries (59%). In general, access to newer and more active therapies such as lenalidomide, thalidomide, doxorubicin, and VELCADE is more difficult in Eastern European countries.

The principal SOC reporting more than 10% higher incidence rates in the SC group when compared to the IV group, was "investigations". This difference was mainly due to "decreased weight" (14% incidence in the SC group vs 2% in the IV group). The incidence of weight decrease was mild to moderate in severity. Overall, body weight data showed that 71% of subjects in the SC treatment group and 69% of subjects in the IV treatment group lost weight during the study. Maximum weight loss of 5% to <10% (Grade 1) was reported in 22 % of subjects in the SC treatment group compared with 16% of subjects in the IV treatment group; this treatment difference was considered by the MAH not clinically relevant.

Besides investigation SOC, significant higher incidence rates in the SC group were observed for adverse events falling in the following SOCs: renal and urinary disorders (e.g. renal failure and impairment) and skin and subcutaneous tissue disorders (e.g. pruritus, rash, pyrexia). While the observed incidence rate of renal and urinary disorders in the IV arm (8%) was lower than the SC arm (14%), it should be noted that this observed incidence rate in the IV arm, based on a total of 86 subjects, was substantially smaller than what was observed in the historical data of IV VELCADE (18%, 243/1356). The 95% confidence intervals for the incidence rate of renal and urinary disorders were 3% to 16% for the IV arm, and 9% to 20% for the SC arm, which obviously overlap. The observed odds

ratio of SC vs. IV was 1.812 favouring the IV arm, and its 95% confidence interval was 0.706 to 5.243, which was quite wide with the lower boundary well below 1 (no difference). Similar arguments can be made for the SOC skin and subcutaneous tissue disorders.

In any case in the next PSURs, a trend analysis of events under SOCs Renal and urinary disorders and skin and subcutaneous tissue disorders and the weight decrease, following IV and SC administration should be performed in order to decide whether to include certain events under strict monitoring.

One case of Hypersensitivity reaction (SOC immune system disorders) was observed in the SC administration, in the pooled analysis between the two studies.

Considering the pharmaceutical form (powder for solution for injection to be reconstituted) and the general precautions needed during preparation of cytotoxic agents, it is very unlikely that Velcade SC could be self-administered at home. As a precautionary measure, to avoid any potential harmful misuse, in the SmPC sections 4.2 and 6.6 of both IV and IV/SC annexes, should be clearly stated that Velcade must be reconstituted by an HCP in hospital.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics and section 4.8 has also been updated in line with the SmPC guideline.

1.6.2. Conclusions on the clinical safety

While safety data in many aspects were similar for the SC and IV administration routes, lower incidences for some relevant bortezomib related adverse events, were noted following SC dosing. The observed reduced risk in peripheral neuropathy associated with the SC route (38% SC vs. 53% IV) was maintained after adjustment for cumulative dose and for region and was also apparent in patients with pre-existing neuropathy. SC administration of VELCADE was locally well tolerated.

Overall, the safety profile of bortezomib was confirmed to be well-characterised notwithstanding the route of administration used. However, since the limited SC use safety database, emerging safety issues could arise in the future.

In the next PSURs, a trend analysis of events under SOCs Renal and urinary disorders and skin and subcutaneous tissue disorders and the weight decrease, following IV and SC administration should be performed in order to decide whether to include certain events under strict monitoring.

1.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Table 23 - Summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities

Important Identified Risks		
Heart failure	Routine pharmacovigilance (as described in Section 2.1)	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. In a single agent Phase 3 randomised, comparative trial the incidence of heart failure in the VELCADE group was similar to that in the dexamethasone group. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored. SmPC: Labelled in Section 4.8 (Undesirable Effects)
Hepatotoxicity	Routine pharmacovigilance (as described in Section 2.1)	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)
Acute hypersensitivity reactions	Routine pharmacovigilance (as described in Section 2.1)	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.
Tumour lysis syndrome	Routine pharmacovigilance (as described in Section 2.1)	The SmPC, Section 4.4 Special Warnings and Precautions for Use, indicates that because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells, the complications of TLS may occur. The patients at risk of TLS are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. SmPC: Labelled in Section 4.8 (Undesirable Effects)
Peripheral motor neuropathy (including paralysis)	Routine pharmacovigilance (as described in Section 2.1)	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that treatment with VELCADE is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. 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	Routine pharmacovigilance (as described in Section 2.1)	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. SmPC: Labelled in Section 4.8 (Undesirable Effects)
Acute diffuse infiltrative pulmonary disease	Routine pharmacovigilance (as described in Section 2.1) Ongoing Japanese Postmarketing surveillance (VEL-PMS-JPN-1) has specific focus on pulmonary complications associated with VELCADE treatment.	SmPC Section 4.3 contraindicates the use of VELCADE in patients with acute diffuse infiltrative pulmonary disease. 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 a pre-treatment chest radiograph. SmPC: Labelled in Section 4.8 (Undesirable Effects)
Pericardial disease	Routine pharmacovigilance (as described in Section 2.1)	SmPC Section 4.3 contraindicates the use of VELCADE in patients with pericardial disease. SmPC: Labelled in Section 4.8 (Undesirable Effects)
Pulmonary hypertension	Routine pharmacovigilance (as described in Section 2.1)	The SmPC, Section 4.8 Undesirable Effects, identifies pulmonary hypertension as a serious adverse reaction uncommonly reported during treatment with VELCADE.
Herpes zoster infection	Routine pharmacovigilance (as described in Section 2.1)	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.
Posterior reversible encephalopathy syndrome (PRES)	Routine pharmacovigilance (as described in Section 2.1)	The SmPC, Section 4.4 Special Warnings and Precautions for Use, warns that there have been reports of PRES in patients receiving VELCADE. PRES is a rare, often reversible, rapidly evolving neurological condition which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging, is used to confirm the diagnosis. In patients developing PRES, VELCADE should be discontinued. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known. SmPC: Labelled in Section 4.8 (Undesirable Effects)
Optic neuropathy, Different degrees of visual impairment (up to blindness)	Routine pharmacovigilance (as described in Section 2.1)	A positive CHMP opinion was received in response to a variation to the Marketing Authorisation for VELCADE was submitted to the EMA in July 2011 to include in the SmPC, Section 4.8 Undesirable Effects optic neuropathy, different degrees of visual impairment (up to blindness) in patients

		receiving VELCADE.
Important Potential Risks		
Ventricular rhythm abnormalities	Routine pharmacovigilance (as described in Section 2.1) Discussed in separate section of the PSUR	The SmPC, Section 4.4 Special Warnings and Precautions for Use, states that there have been isolated cases of QT-interval prolongation during treatment with VELCADE. SmPC: Arrhythmia and ventricular dysfunction are labelled in Section 4.8 (Undesirable Effects)
Guillain-Barré Syndrome	Routine pharmacovigilance (as described in Section 2.1) Discussed in separate section of the PSUR	None
Progressive multifocal leukoencephalopathy	Routine pharmacovigilance (as described in Section 2.1) Discussed in separate section of the PSUR	None
Other central nervous system disorders	Routine pharmacovigilance (as described in Section 2.1) Discussed in separate section of the PSUR	SmPC: encephalopathy is labelled in Section 4.8 (Undesirable Effects).
Medication/Dispensing errors	Routine pharmacovigilance (as described in Section 2.1) Discussed in separate section of the PSUR	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. The SmPC in Sections 4.2, 4.4 and 6.6 include warnings regarding the danger of intrathecal administration which may result in death Additional Activities include: Single vial packaging, labelling for guidance against dosing and administration errors will be added on the vial label and single labelling for IV and SC routes of administration. Educational plan: Training of HCPs (particularly oncologists, haematologists, haematology nurses, oncology nurses, hospital pharmacists, and other specialised personnel in charge of preparing chemotherapeutic drugs) on approved professional labelling; the SmPC, a reconstitution, dosing and administration booklet with focus on potential risk for medication/dispensing error, a reconstitution poster and a dosing slide rule. Training of Company medical representatives and MSLs.
Important Missing Information		
Safety in patients with cardiac impairment or with NYHA Class III or IV impairment	Routine Pharmacovigilance Discussed in separate section of the PSUR	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.

Safety in patients with ECOG>2	Routine Pharmacovigilance Discussed in separate section of the PSUR	None

The following additional risk minimisation activities were required:

- Medication/Dispensing Error Educational Programme for HCPs

Prior to launch of VELCADE 3.5mg new dual route of administration (subcutaneous and intravenous) package, in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the national competent authority.

The MAH shall ensure that, at launch of VELCADE 3.5mg new dual route package and thereafter, all healthcare professionals involved in the prescribing, dispensing, handling or administration of VELCADE 3.5mg are provided with educational material.

The educational material shall consist of the following:

- SmPC
- Reconstitution, dosing and administration booklet
- Reconstitution poster
- Dosing Slide Rule

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

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

The Reconstitution poster shall contain the following key elements:

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

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

Dosing Slide Rule shall contain the following key elements:

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

1.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2. Benefit-Risk Balance

Benefits

Beneficial effects

The proposed SC route of administration represents a valuable alternative to IV injections that are inconvenient for patients with poor vein access.

Bioequivalence in terms of systemic exposure, measured as AUC, between the SC and IV routes was demonstrated mainly by a dedicated randomised phase 1 PK/PD study (CAN-1004) involving patients with relapsed multiple myeloma after at least 1 prior treatment but naïve to Velcade. Both plasma concentration and proteasome inhibition activity were comparable.

Efficacy of the SC administration was demonstrated in the pivotal phase 3 study MMY-3021.

Compared to IV administration, Velcade given SC was non-inferior in terms of Overall Response Rate after 4 cycles (ORR 42% for both IV and SC routes). These results are in line with historical data of single-agent Velcade and are consistent with results from 1-year OS and PFS provided.

Results from secondary efficacy endpoints also confirm that Velcade behaves in a similar way notwithstanding the administration route.

Uncertainty in the knowledge about the beneficial effects.

The Primary Efficacy Endpoint of the pivotal trial MMY-3021, was ORR after 4 cycles, which is not ideal but since consistent results were obtained for the secondary efficacy endpoints, in particularly One year survival and PFS, this is not a concern.

Based on the immaturity of survival data (32% of death events observed) and the rate (27.5%) of patients censored for progression events, efficacy results of Study MMY-3021 cannot be seen as final.

Results for secondary endpoints were similar in both arms, albeit high rate of censored patients, TTP (53%), PFS (40%), 1-year survival rate (73%). Time and reason of censoring for disease progression, PFS and OS seems to be balanced between the two arms.

The non-inferiority margin of 60% may potentially leaving uncertainties on the estimated efficacy. However, given the context of this particular non inferiority setting in which the same active substance is given by different routes of administration and PK data have confirmed similar overall exposure between IV and SC use, the point estimates, ORR both 42% for IV and SC use, can be considered reassuring as opposed to a formal conclusion of the non-inferiority.

Risks

Unfavourable effects

Both studies CAN-1004 and MMY-3021 showed similar patterns of incidence of adverse events and adverse events leading to treatment discontinuation associated with SC and IV administration.

Overall, the SC administration of Velcade was well tolerated, it showed an improved systemic safety profile when compared to the IV route with an acceptable local tolerability.

In particular, one of the main safety results of the study was a lower incidence of peripheral neuropathy Grade ≥2 in the SC group with a ≥10% difference (33% SC vs. 44% IV). The observed reduced risk in peripheral neuropathy associated with the SC route was maintained after adjustment for cumulative dose and for region and was also apparent in patients with pre-existing neuropathy. Also the incidence of diarrhoea was decreased following SC vs IV administration (25% SC vs. 40% IV).

Among the adverse events with a frequency higher than 10% in either treatment group IV and SC, were weight decrease and renal and urinary disorders (e.g. renal failure and impairment) (14% vs. 8%) and skin and subcutaneous tissue disorders (e.g. pruritus, rash, pyrexia) (24% vs. 19%).

One non serious case of hypersensitivity reactions (SOC immune system disorders) was observed in the SC administration, in the pooled analysis between the two studies.

Uncertainty in the knowledge about the unfavourable effects

The size of the safety database for SC administration is limited to 159 patients (Study CAN-1004 N=24; 12 IV + 12 SC - Study MMY-3021 N=221; 74 IV + 147 SC). A Risk Management Plan is in place in order to adequately monitor any newly emerging safety signals.

In the next PSURs, a trend analysis of events under SOCs Renal and urinary disorders and skin and subcutaneous tissue disorders and the weight decrease, following IV and SC administration should be performed in order to decide whether to include certain events under strict monitoring.

Velcade is available as 3.5 mg and 1.0 mg vials. Only the 3.5 mg vial is to be used for SC injection to be reconstituted at a different concentration than for IV use. Therefore, there may be a potential for errors in reconstitution and in the route of administration. Furthermore, reports of fatal inadvertent administration errors via intrathecal route have been reported. As a consequence, a dual route (IV/SC) 3.5 mg packaging with a concertina (flag) vial label, was clearly needed to report the reconstitution instructions for both IV and SC use (i.e., ml of sodium chloride 9 mg/ml to add and the amount per unit volume, 1 mg/ml for IV and 2.5 mg/ml for SC) and a warning regarding the route of administration. As a consequence a concertina (flag) vial label has been introduced. Furthermore, additional risk minimisation activities through educational materials for healthcare professionals as described in the RMP are needed in order to mitigate potential risk medication/dispensing error. Besides the SmPC, a Reconstitution, Dosing and Administration Booklet, a Reconstitution Poster visually describing the reconstitution instructions for Velcade IV and SC administrations to be affixed in the hospital units and a Dosing Slide Rule to determine the appropriate VELCADE dose were agreed.

Moreover, training of HCPs (particularly oncologists, haematologists, haematology nurses, oncology nurses, hospital pharmacists, and other specialised personnel in charge of preparing chemotherapeutic drugs) on approved professional labelling, is considered in the objectives of Bortezomib Educational Program in Europe.

Benefit-risk balance

Importance of favourable and unfavourable effects

Given the equivalent systemic exposure and non-inferior efficacy demonstrated in the treated population, the treatment efficacy is expected to be the same for SC and IV administration in all the patient populations and indications for which VELCADE is administered at a dose of 1.3 mg/m2 using the currently approved dosing schedule.

Moreover, the new SC method of administrating bortezomib can be a valid option to treat patients with poor venous approach.

While safety data in many aspects were similar for the SC and IV treatment groups, lower incidences for some relevant safety parameters were noted in the SC treatment group. The reduced risk in peripheral neuropathy associated with the SC route was maintained after adjustment for cumulative dose and for region and was also apparent in patients with pre-existing neuropathy. This is of importance as neurotoxicity is a problematic issue with almost all effective drugs available for patients and peripheral sensory neuropathy has been the main reason for dose modification or treatment discontinuation in the current clinical practise.

Subcutaneous administration of VELCADE was locally well tolerated. The majority of local injection site reactions were redness, of mild or moderate intensity, and resolved in all cases.

Benefit-risk balance

SC administration was shown to have similar efficacy and safety profiles as the IV administration. The SC route of administration is considered an additional tool to potentially improve patient compliance and treatment efficacy in a patient population that is not suitable for IV administration particularly in patients with poor venous access. However, since the safety database on the use of the SC route is small, risk minimisation measures are proposed to monitor emerging safety issues that could arise particularly potential medical errors.

Discussion on the benefit-risk balance

Taken together, the benefits of the proposed subcutaneous administration of bortezomib outweigh the risks associated with this new route of administration.

3. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Velcade is not similar to Revlimid and Thalidomide Celgene within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Velcade 3.5mg powder for solution for injection for subcutaneous use, as monotherapy for the treatment of 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 and in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant, is favourable and therefore recommends the granting of the extension of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs
The PSUR cycle for the medicinal product should follow the a half-yearly cycle until otherwise agreed by the CHMP

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

Prior to launch of VELCADE 3.5mg new dual route of administration (subcutaneous and intravenous) package, in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the national competent authority.
The MAH shall ensure that, at launch of VELCADE 3.5mg new dual route package and thereafter, all healthcare professionals involved in the prescribing, dispensing, handling or administration of VELCADE 3.5mg are provided with educational material.

The educational material shall consist of the following:

- SmPC
- Reconstitution, dosing and administration booklet
- Reconstitution poster
- Dosing Slide Rule

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

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

The Reconstitution poster shall contain the following key elements:

- different reconstitution requirements for VELCADE 3.5mg IV or SC use
- need to handling the medicinal product in sterile setting
- storage precautions for reconstituted solution
- advice on how to reduce the risk of mix-up of IV and SC reconstituted syringes
- that VELCADE is to be given only by IV or SC injections; no other route of administration is allowed
- that VELCADE 1mg is only for IV use
- to report any adverse event, or medication error experienced with the administration of VELCADE 3.5mg

Dosing Slide Rule shall contain the following key elements:

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

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

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

Prior to launch of VELCADE 3.5mg new dual route of administration (subcutaneous and intravenous) package, in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the national competent authority.
The MAH shall ensure that, at launch of VELCADE 3.5mg new dual route package and thereafter, all healthcare professionals involved in the prescribing, dispensing, handling or administration of VELCADE 3.5mg are provided with educational material.

The educational material shall consist of the following:

- SmPC
- Reconstitution, dosing and administration booklet
- Reconstitution poster
- Dosing Slide Rule

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

The Reconstitution poster shall contain the following key elements:
- different reconstitution requirements for VELCADE 3.5mg IV or SC use
- need to handling the medicinal product in sterile setting
- storage precautions for reconstituted solution
- advice on how to reduce the risk of mix-up of IV and SC reconstituted syringes
- that VELCADE is to be given only by IV or SC injections; no other route of administration is allowed
- that VELCADE 1mg is only for IV use
- to report any adverse event, or medication error experienced with the administration of VELCADE 3.5mg

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