



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Bortezomib

Proprietary Product Name: Velcade

Sponsor: Janssen-Cilag Pty Ltd

January 2013

TGA Health Safety
Regulation

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I. Introduction to product submission

Submission details

<i>Type of Submission</i>	Major variation (new route of administration; subcutaneous (SC) injection).
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	2 July 2012
<i>Active ingredients:</i>	Bortezomib
<i>Product Names:</i>	Velcade
<i>Sponsor's Name and Address:</i>	Janssen-Cilag Pty Ltd. 1-5 Khartoum Road, Macquarie Park, NSW 2113, Australia.
<i>Dose form:</i>	Powder for injection
<i>Strength:</i>	3.5 mg
<i>Container:</i>	vial
<i>Pack size:</i>	one
<i>Approved Therapeutic use:</i>	<p><i>Velcade, in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy.</i></p> <p><i>Velcade, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.</i></p> <p><i>Velcade, is also indicated for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.</i></p>
<i>Route of administration:</i>	Intravenous (IV) injection
<i>Dosage:</i>	See below
<i>ARTG Number:</i>	104542

Product background

Bortezomib is an anticancer agent which acts through inhibition of the proteasome, an intracellular protein complex which is responsible for the degradation of cellular proteins.

Inhibition of the proteasome results in decreased degradation of I κ -B, an inhibitory protein. I κ -B inhibits the actions of nuclear factor- κ B (NF- κ B), a transcription factor which promotes cell proliferation and blocks cell death pathways.

Bortezomib is presently approved for use in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not suitable for high dose chemotherapy. Bortezomib is also indicated for the treatment of multiple myeloma patients who have received at least one prior therapy and who have progressive disease.

This submission involves a proposal for registration of a subcutaneous (SC) route of administration and does not involve changes to the present indications.

The currently approved route of administration is via intravenous (IV) administration. The approved dosage regimens are summarised in Table 1:

Table 1. Bortezomib currently approved dosage regimens

Setting	Combined with	Cycles	Bortezomib Dose	On Days	Cycle length
1 st line – eligible for HDC / ASCT	Thalidomide + Dexamethasone	Cycles 1 to 3	1.3 mg/m ²	1, 4, 8, 11	21 days
	Dexamethasone	Cycles 1 to 4	1.3 mg/m ²	1, 4, 8, 11	21 days
1 st line – Not eligible for HDC / ASCT	Melphalan + Prednisone	Cycles 1 to 4	1.3 mg/m ²	1, 4, 8, 11, 22, 25, 29, 32	42 days
		Cycles 5 to 9	1.3 mg/m ²	1, 8, 22, 29	42 days
2 nd line	-	Cycles 1 to 8	1.3 mg/m ²	1, 4, 8, 11	21 days
		Cycles 9+	1.3 mg/m ²	1, 8, 15, 22	35 days

ASCT: autologous stem cell transplantation
HDC: high dose chemotherapy

The current application seeks approval for use of the SC route of administration, using the same dosage regimens. For IV administration the product is reconstituted to a concentration of 1.0 mg/mL. For SC administration, reconstitution to a higher concentration (2.5 mg/mL) is proposed.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 14 February 2006. Bortezomib for administration by SC injection is approved in the USA (January 2012) and Canada (March 2012); similar applications have been submitted to approximately 30 additional countries, including the UK, Sweden and New Zealand.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Janssen-Cilag Pty Ltd proposes to register a new route of administration (SC injection) for their Velcade 3.5 mg bortezomib powder for injection, which is currently approved for IV use. Janssen-Cilag's other registered Velcade product, a 1 mg bortezomib powder for injection, is not part of this application.

No changes appear to have been made to the manufacture and quality control of the drug substance or drug product.

The instructions for the currently registered powder for IV injection require that it is reconstituted in normal saline to give a bortezomib concentration of 1 mg/mL (that is, 3.5 mL of normal saline is added to the powder in the vial). For the proposed SC injection the product is reconstituted with normal saline to give a concentration of 2.5 mg/mL (that is, 1.4 mL of normal saline is added to the contents of the vial). It was unclear if the delivered doses then differ significantly. In response to a request from TGA for information on this aspect, the sponsor provided data on the extractable volume obtained with the different reconstitution volumes. The residual drug is similar with both (about 0.1 mg). This is acceptable.

The maximum daily dose is 1.3 mg/m² administered on Days 1, 4, 8 and 11 of a 21 day treatment cycle. The maximum dose equates to a daily dose of 1.56-2.86 mg (assuming a body surface area of 1.2-2.2 m²).

Data were supplied to demonstrate the stability of the 2.5 mg/mL reconstituted solution when it was stored in the proposed vials as well as in syringes obtained from a variety of suppliers. In each case the reconstituted solution was stored at 5°C (24 h; protected from light) and at 25°C (24 h; exposed to ambient light). The product met specification limits under all conditions tested and on the basis of these results the sponsor has proposed a maximum storage time of 8 h for the reconstituted drug product stored at ambient conditions in either vials or syringes. No other chemistry or quality data were supplied.

Biopharmaceutics

Two studies, designated CAN-1004 and MMY-3021, were provided in which the human pharmacokinetics (PK) of the proposed SC injection were compared with the approved IV injection. These studies provide information on absolute bioavailability after SC dosing.

Study CAN-1004

The primary objective of Study CAN-1004 was to characterise the PK of the two routes of administration. It was a randomised, open label, Phase I, multicenter, parallel group study in which 24 patients with relapsed/refractory multiple myeloma received IV or SC injections of bortezomib 1.3 mg/m² on Days 1, 4, 8, and 11 of a 3 week cycle for up to 8 cycles. The administered injection concentration was 1 mg/mL (more dilute than proposed for SC dosing). Bortezomib concentrations in plasma were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Twenty subjects (10 IV and 10 SC) were evaluable for PK analysis.

There is a very large difference in maximum plasma bortezomib concentrations (C_{max}), as expected. Results from the study (summarised in the Table 2, below) revealed that C_{max} was lower (94% lower on Day 1 and 86% lower on Day 11) and occurred later, with the time to C_{max} (T_{max}) of 0.5 h for SC administration relative to IV administration.

Table 2. Summary of bortezomib PK parameters following IV or SC administration of Velcade 1.3 mg/m² on Days 1 and 11 of Cycle 1.

(Study CAN-1004)				
Parameter	Day 1		Day 11	
	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)

There is marked accumulation over ten days dosing, consistent with a relatively long half life (range 65.7 to 98.1 h).

The sponsor's statistical analysis was done using an analysis of variance (ANOVA) model for inter-treatment comparisons of the bortezomib PK parameters C_{max}, area under the curve from time 0 to the last quantifiable time (AUC_{last}), and AUC over time 0 to infinity (AUC_{0-∞}). The findings are summarised in Table 3, below. A clear difference is seen on assessment of mean plasma C_{max} values after SC administration compared with IV administration on both Day 1 and Day 11 (p < 0.001 on log scale). Differences in systemic bortezomib exposure (as AUC_{0-∞} or AUC_{last}) between the IV and the SC groups were less marked:

Table 3. Summary of analysis for bortezomib PK parameters.

(Study 26866138-CAN-1004)									
Day	Type	Parameter	SC		IV		SC-IV		p-value
			N	LS mean	N	LS mean	Diff.	95% CI	
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

The relative SC bioavailability was 82.5% on Day 1 and 99.0% on Day 11. The sponsor avoids reporting planned 90% confidence intervals (CIs), but it appears that the two injection routes would not be formally bioequivalent (the sponsor concludes "no significant difference could be seen between the means of the PK parameters AUC_{0-∞} and AUC_{last} in the IV and the SC groups", which is a much weaker statistical test).

Study MMY-3021

Study MMY-3021 was a randomised, open-label, multicenter, Phase III, parallel group study in adults diagnosed with multiple myeloma who had received 1 to 3 prior lines of therapy and had measurable disease and evidence of disease progression since their last prior therapy. Subjects were randomised to receive bortezomib 1.3 mg/m² administered by SC injection or IV injection on Days 1, 4, 8, and 11 of a 3 week cycle for 8 cycles.

The administered bortezomib injection concentration was 2.5 mg/mL for SC administration (as proposed) and 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 pharmacodynamic; PD) analyses were collected predose only on Day 1, but at '0'

(immediately before dosing) and 2, 5, 15, and 30 min, and 1, 2, 4, 6, 10, 24, 32, 48 and 72 h after dosing on Day 11 of Cycle 1.

Following SC administration, bortezomib C_{max} was approximately 10 times lower than that of the IV, with a short median T_{max} of 0.5 h (see Table 4, below). Bortezomib concentration-time profiles during the terminal elimination phase were similar following each treatment. The extrapolated part of $AUC_{0-\infty}$ was more than 20, so only AUC_{last} was reported by the sponsor. Bortezomib systemic exposure (AUC_{last}) 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 80.2% to 122.8%; that is, just within the standard 80-125% bioequivalence criteria.

Table 4. Summary of bortezomib PK parameters following IV or SC administration of Velcade 1.3 mg/m² on Day 11 of Cycle 1. Study MMY-3021

Parameter	Treatment	
	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)

No clear effect of the different SC injection concentrations is apparent by comparison of profiles in Study CAN-1004.

Labels and Product Information

The evaluator recommended the sponsor make several revisions to the labelling and PI for Velcade. Details of these are beyond the scope of this AusPAR.

Advisory committee considerations

This application was not referred for advice from the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

The sponsor's responses to questions raised by the evaluator and the revised labels and PI documents were acceptable with respect to chemistry and quality control matters.

Approval was recommended with respect to chemistry and bioavailability aspects.

III. Nonclinical findings

Introduction

Nonclinical data to support this application consisting of the following studies:

- PK/PD ; 2 studies
- Repeat dose toxicity; 3 studies in non-human primates
- Local tolerance; 1 study in rabbits

These have provided adequate information to support the application for SC administration of bortezomib. The animal studies were satisfactorily designed, with a majority of the studies compliant with Good Laboratory Practice (GLP) requirements.

Pharmacokinetics/Pharmacodynamics

Absorption of bortezomib appeared to be rapid after single and repeat dose SC administration in animal studies. The SC administration was similarly comparable with the IV administration in the pivotal repeat dose PK study. Both plasma C_{max} and AUC values were higher after repeat dose compared with single dose administration for both SC and IV administration. After single dose administration, the AUC values for SC and IV administration were comparable in whole blood. However, for reasons unknown, the AUC values in plasma after Day 1 for bortezomib were higher after SC administration compared with IV.

In the pivotal study, bortezomib was administered SC or IV at a similar dose (0.1 mg/kg [1.2 mg/m²]) to Cynomolgus monkeys, allowing direct comparison of the PK and PD data as well as producing results comparable to the clinical data studies submitted. Comparison of the plasma exposure of bortezomib after SC administration in monkeys and humans produced an exposure ratio slightly higher than 1 (Table 5). The results indicated that, in both species, bortezomib exposure following SC dosing was fairly comparable to that achieved following IV administration. The nonclinical pivotal study showed similar levels of 20S proteasome activity¹ inhibition, with a delay in maximal inhibition after SC administration compared with IV administration. The maximal proteasome inhibition after SC repeat dose administration remained comparable to repeat dose IV administration (Table 5). The results from non-human primates were comparable to the clinical study data in humans with multiple myeloma at similar doses. The data indicate a similar PK/PD profile with SC and IV dosing.

¹ The 20S proteasome inhibition defines the pharmacodynamic response by calculating the specific activity value of the chymotryptic rate expressed per second and per milligram of protein, while comparing the results with the pre-dose proteasome activity set at 100%.

Table 5. Plasma exposure comparison of bortezomib in monkeys and humans after SC administration

Species (strain) Study no.	Dose (mg/m ²)	Dose (mg/mL)	Plasma Kinetics			20S Proteasome Inhibition	
			C _{max} [#] (ng/mL)	T _{max} [†] (h)	AUC (ng·h/mL)	E _{max} [*] (%)	AUE _{72h} (%·h)
Monkey (Cynomolgus) Study TOX7345 Cycle 4, day 74 <i>n</i> =3 per sex/group	1.2	3.5	113	0.117	211	71.0	1454
Human Study CAN-1004 Cycle 1, day 11 <i>n</i> =10	1.3	2.5	22.5	0.500	195	57.0	1619
Human Study MMY-3021 Cycle 1, day 11 <i>n</i> =17	1.3	2.5	20.4	0.500	155	63.7	1714

#Median concentration at the first time point for IV; †Time when C_{max} is first observed. *Observed mean maximum protease inhibition

Toxicology

Repeat-dose toxicity

The toxicity of bortezomib after SC administration was characterised in repeat-dose toxicity studies in non-human primates and compared with IV administration. The toxicity data for bortezomib using twice weekly administration in Cynomolgus monkeys indicate a comparable toxicological profile for the IV and SC routes of administration. The histopathological changes seen at a high SC dose (0.166 mg/kg/week) are consistent with the previously reported toxicities for bortezomib, and included nerve fibre degradation (peripheral nervous system and spinal cord), cortical tubular degradation/hypertrophy in the kidneys, as well as changes in bone marrow (hypocellularity) and lymph nodes (atrophy).

Local tolerance

The local tolerability of SC administration was assessed following single dosing to rabbits. There were no notable differences in reactions following SC injection of 1.0 mg/mL bortezomib and 3.5 mg/mL bortezomib, indicating that the higher concentration of bortezomib was well tolerated. Following repeated administration to Cynomolgus monkeys, there were no significant signs of irritation or test article-related microscopic

changes at SC injection sites, indicating that the bortezomib formulation (at a concentration of 3.5 mg/mL) was well-tolerated following repeated dosing. Cynomolgus monkeys receiving repeated IV injection of 1.0 mg/mL bortezomib had a higher incidence of oedema and erythema at the injection site compared to SC administration.

Nonclinical summary and conclusions

- There were no major deficiencies in the nonclinical data. All studies referred to SC administration route and 2 studies compared the PK/PD and/or toxicological effects following SC administration with the clinically approved IV administration of bortezomib.
- The studies submitted have shown that SC administration of 3.5 mg/mL of bortezomib produces PK, PD and toxicological results comparable to IV administration. In addition, SC administration at this concentration has been shown to have no clinically related observations in the local injection area and appears to be well tolerated.
- The suggested increased concentration of bortezomib for SC administration (2.5 mg/mL) compared to the clinically approved concentration for IV administration (1.0 mg/mL) is considered acceptable from a toxicological perspective.

Conclusion

There were no nonclinical objections to registering SC injection as a new route of administration of bortezomib (Velcade).

IV. Clinical findings

Introduction

In the first line setting, bortezomib is presently approved for IV administration in a dose of 1.3 mg/m² on Days 1 and 4, 8 and 11 of the first 2 weeks, then a rest period for the third, followed by twice weekly for 2 weeks and a rest period for 1 week. This regimen is repeated for 4 cycles. This is followed by once weekly administration (Days 1, 8, 22 and 29 of a 6 week cycle) for a total of five further cycles. A total of 9 cycles of administration can be undertaken. The present submission proposes SC administration of bortezomib for the same dosage strengths and schedule.

Clinical rationale

Bortezomib is currently approved for IV administration and, as preclinical studies have indicated that SC administration provides similar bioavailability, it is proposed that SC administration be considered for patients in whom prolonged therapy might be required, IV access is difficult, or there are accessibility problems.

Formulation

There have been no changes in relation to the formulation of the vials, which would be available for either IV or SC administration. The only change would be that the concentration for administration would be different, being 1 mg/mL for the IV bolus administration and 2.5 mg/mL for SC administration.

Scope of the clinical dossier

The clinical part of the submission contains relevant data in relation to two clinical studies, the pivotal Study MMY-3021, which was an open label, randomised study of SC or

IV bortezomib in subjects with previously treated multiple myeloma. This is an international multicentre study comparing efficacy, safety and PK/PD data for SC versus IV bortezomib.

The supportive study is a pilot trial comparing the PK and PD of SC versus IV administration of bortezomib in patients with multiple myeloma. It was a Phase I, randomised, open-label, multicentre study.

Pharmacokinetics/Pharmacodynamics

In this submission the PK and PD profiles of bortezomib administered by the IV and SC routes were investigated as the primary objective of Study CAN-1004, involving 20 evaluable patients, and also as a sub-study of the pivotal Study MMY-3021 involving 31 evaluable subjects. The patients in both studies received bortezomib either by IV or SC administration at the starting dose of 1.3 mg/m² on Days 1, 4, 8 and 11 of a 3 week Cycle.

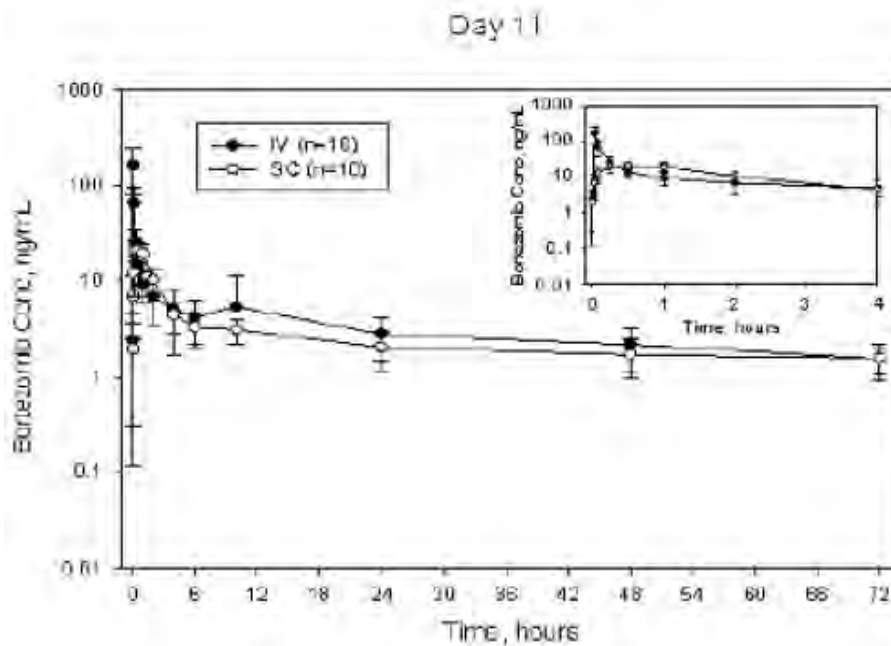
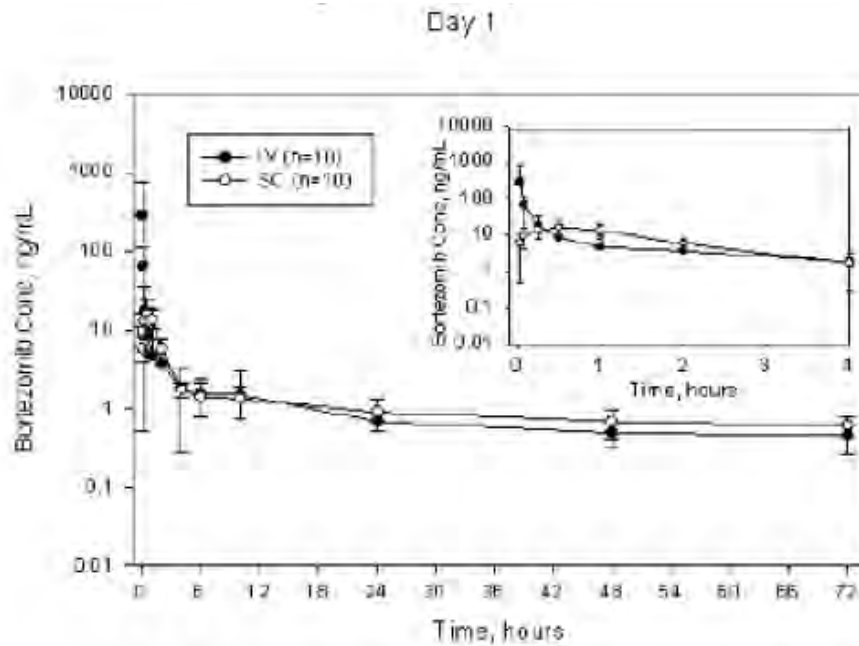
In Study CAN-1004, the characterisation of the PK and PD profiles of bortezomib began on Day 1 and Day 11 of Cycle 1, and in Study MMY-3021 these profiles were characterised on Day 11 of Cycle 1. In both studies, bortezomib plasma concentrations and proteasome activity were determined by the same laboratories that developed methodologies previously used in the bortezomib development programme. In both studies, PK and PD profiling occurred during Cycle 1 with single agent bortezomib.

For PK analyses, bortezomib plasma samples were analysed using a validated LC-MS/MS assay and PK parameters were calculated using conventional non-compartmental methods. In relation to PD measurement, that is, proteasome inhibition, whole blood samples were analysed to determine the chymotryptic activity of the proteasome using the established method based on fluorometric measurement of the rate at which proteasome hydrolyses the amide bond in small peptide substrates. Bortezomib PD parameters (T_{max} , E_{max} and area under the effect-time curve; AUE) were calculated by analysis of the percent inhibition of 20S proteasome activity over time data.

Study CAN-1004

In this study, 10 patients were randomised to receive the IV or SC route of administration, respectively. With SC administration, the plasma bortezomib C_{max} was lower (94% lower on Day 1 and 86% lower on Day 11) and this occurred later (T_{max} 0.5 h) relative to IV administration. However bortezomib systemic exposure (AUC) following SC administration was comparable to that after IV administration: the statistical significance probability (p) value was 0.11 after single dosing and 0.64 after repeated dosing. These findings are depicted in Figure 1, below.

Figure 1. Mean (SD) plasma bortezomib concentration-time profile following IV or SC injection of Velcade 1.3 mg/m² on Days 1 and 11 (log-linear scale)



After repeat doses, bortezomib exhibited similar systemic clearances for the SC and IV groups. After a single dose, the mean volume of distribution was high, indicating that bortezomib distributes extensively into peripheral tissues. The mean terminal half-life range was 65.7-98.1 h and was similar for both routes of administration, *albeit* with high inter-subject variability.

In relation to PD, more than 90% of subjects had > 50% proteasome inhibition in whole blood at any time following single and multiple doses. Reversibility of proteasome inhibition was demonstrated, as proteasome activity was inhibited by approximately 50% relative to baseline at 72 h after the last administered dose. In general, there were no statistically significant differences observed in mean values of PD-time profiles (that is, AUE_{last}) between treatment groups. The overall effect of proteasome inhibition over time was similar for bortezomib administered by the SC and IV routes and is summarised in Table 6, below.

Table 6. Summary of bortezomib PD parameters following IV or SC administration of Velcade 1.3 mg/m² on Days 1 and 11 of Cycle 1.

Parameter	(Study CAN-1004)			
	Day 1		Day 11	
	IV (n=10)	SC (n=10)	IV (n=10)	SC (n=10)
T _{max} (h) ^a	0.03 (0.03-0.97)	2.02 (0.57-4.00)	0.05 (0.03-0.50)	2.00 (1.00-4.00)
E _{max} (%)	71.3 (7.28)	57.7 (11.8)	68.8 (6.49)	57.0 (12.8)
AUE _{last} (%.h)	1297 (734)	822 (542)	1283 (595)	1619 (804)

AUE_{last}=area under the percent inhibition-time curve from time 0 to the time of last quantifiable concentration; E_{max}=observed maximum percent inhibition of 20S proteasome activity; h=hours; IV=intravenous; SC=subcutaneous; SD=standard deviation; T_{max}=time when E_{max} is first observed
Values are Mean (standard deviation)
^a Median (range)

The mean observed percent inhibition of proteasome activity relative to baseline in whole blood following administration of bortezomib ranged from 33.4%-77.7% for the SC group and from 60.1%-86.5% for the IV group. After multiple doses, on Day 11, the average maximum percent inhibition of proteasome activity observed following administration of bortezomib was 57% and 68.8% for the SC and IV groups, respectively.

Evaluator's comment: Bortezomib systemic exposure and PD parameters after SC injection in this study indicate that they were generally comparable to that after the IV bolus injection in subjects with previously treated multiple myeloma.

Study MMY-3021

This study included a sub-study involving 31 subjects enrolled in a PK/PD analyses, with 17 in the SC treatment group and 14 in the IV treatment group.

Following SC administration of bortezomib, C_{max} was approximately 10 times lower than that after the IV dose, with a short median T_{max} of 0.5 h. The bortezomib concentration-time profile during the terminal elimination phase was similar following each treatment. Bortezomib systemic exposure (AUC) following SC injection was equivalent to that after IV injection, with a geometric mean ratio (SC to IV) of 0.992 and 90% CI of 80.18-122.8% (see Table 4, above, for PK data from this study).

In relation to the PD results, the mean observed maximum percent inhibition of 20S proteasome (E_{max}) was comparable for the SC and IV groups, being 63.7% versus 69.3%, respectively, following multiple 1.3 mg/m² SC or IV doses. Mean AUE over 72 h (AUE_{72h}) after SC injection was comparable to that after the IV injection and within the observed variability (coefficient of variation (CV) = 36-55%). These findings are shown in Table 7 below.

Table 7. Summary of bortezomib PD parameters following IV or SC administration of Velcade 1.3 mg/m² on Day 11 of Cycle 1.

Parameter	(Study 26866138-MMY-3021)	
	Treatment	
	IV (n=14)	SC (n=17)
T _{max} (h) ^a	0.08 (0.03-0.5)	2.00 (0.5-24)
E _{max} (%)	69.3 (13.2)	63.7 (10.6)
AUE ₇₂ (h.%)	1383 (767)	1714 (617)

AUE₇₂=area under the percent inhibition-time curve from time 0 to 72 hours; E_{max}=observed maximum percent inhibition of 20S proteasome activity; h=hours; IV=intravenous; SC=subcutaneous; SD=standard deviation; T_{max}=time when E_{max} is first observed
Values are Mean (standard deviation)
^a Median (range)

In addition, an exploratory analysis shows that there are no apparent differences in bortezomib exposure due to the SC injection site, that is, abdomen or thigh; E_{\max} and AUE_{72h} were also comparable for both injection sites.

Evaluator's comment: These data also confirm the PK/PD comparability between SC and IV administration.

Efficacy

Two studies in this submission provided data in relation to efficacy: pivotal Study MMY-3021 and the supportive Phase I Study CAN-1004.

Dosage selection for the pivotal studies

In the studies undertaken in this submission, the dose selected for SC administration was comparable to that for that previously approved IV administration, namely 1.3 mg/m². This is based on the comparability in PK and PD data, presented above, as well as earlier nonclinical data.

Pivotal Study MMY-3021

Design

Study MMY-3021 was a randomised, open-label, international, multicentre Phase III study, which evaluated bortezomib in patients with multiple myeloma who had received 1-3 prior lines of therapy and had measurable disease and evidence of disease progression since the last previous therapy. Subjects were randomly assigned in a 2:1 ratio to receive 1.3 mg/m² of bortezomib by either SC or IV injection, and were stratified by the number of lines of prior therapy (1 versus > 1) and disease Stage according to the International Staging System (ISS) for multiple myeloma (incorporating β_2 microglobulin and albumin levels; Stages I, II and III). The planned total sample size was 216 subjects: 144 in the SC treatment group and 72 in the IV treatment group. The study consisted of 3 phases: screening phase, open-label treatment phase, and a post-treatment follow-up phase.

Objectives

The primary objective of the study was to compare the overall response rate (ORR), defined as the proportion of subjects with complete response (CR) or partial response (PR), after 4 cycles of SC or IV administered bortezomib, in patients with previously treated multiple myeloma.

Secondary objectives were to determine: the CR, near CR (nCR) and very good PR (VGPR) rates after 4 cycles of single agent bortezomib; the ORR after 8 cycles, including the effect of adding dexamethasone; the duration of the response; the time to tumour progression; progression free survival (PFS); one year survival; and time to response following bortezomib therapy.

Treatment

During the 21 day screening phase, patient eligibility was confirmed and patients were then randomly assigned to receive either SC or IV bortezomib.

During the 24 week open-label treatment phase, patients received bortezomib on Days 1, 4, 8 and 11 of a 3 week cycle for 8 cycles. If, by investigator assessment, after 4 cycles of therapy the patient had no change or had PR as the best response and had not progressed, then an additional 4 cycles of bortezomib could be given, but at the discretion of the investigator, and dexamethasone could be added to this treatment regimen. Dexamethasone was to be administered orally (PO) at a dose of 20 mg on the day of and

the day after bortezomib dosing. Patients with progressive disease discontinued treatment at the time progressive disease was confirmed.

Patients who had stable disease or PR as best ORR at the end of Cycle 8 but who were evolving steadily to a late PR or CR, respectively, could receive 2 additional cycles of study medication.

In the post-treatment follow-up phase, patients who had not progressed were to be assessed every 8 weeks until progressive disease was recorded. Thereafter, patients were to be assessed every 12 weeks for survival and subsequent therapy.

Assessments

Disease response was measured according to the modified European Group for Blood and Bone Marrow Transplantation (EBMT) criteria, with the addition of PR sub-categories of nCR (incomplete remission) and VGPR (very good partial remission).

Efficacy assessments included monoclonal protein (M-protein) measurements in serum and 24 h urine, bone marrow examination, skeletal survey, documentation of extramedullary plasma cytomias, and serum calcium adjusted for albumin.

An overview of efficacy evaluations and assessment schedule for the determination of disease progression is given in Table 8, below.

The evaluation of efficacy included the determination of non-inferiority between the two treatment arms; non-inferiority was defined as SC administration retaining 60% of the IV treatment effect, as measured by the ORR. Assuming the overall response rate was 35.5% for both treatment groups, a one-sided alpha level of 0.025 and approximately 80% power, approximately 216 patients (144 SC, 72 IV) were needed to show non-inferiority.

Table 8. Overview of efficacy evaluations and assessment schedule for determination of disease progression.

(MMY-3021)		
Efficacy Evaluation	Screening/Treatment Phase	Follow-up Phase
Quantitation of Ig in serum, M-protein in serum and 24-hour urine by protein electrophoresis, serum Freelite chain assay, and IF (by central laboratory)	Screening phase for all subjects Treatment phase for all subjects. Assessments were performed every 3 weeks during the 24-week treatment phase and at the end-of-treatment visit.	Every 8 weeks until development of PD
Serum calcium corrected for albumin (by local laboratory).		
Bone marrow aspirate/biopsy	Screening phase for all subjects Treatment phase: Assessments were performed only to confirm CR or PD	Assessments were performed only to confirm CR or PD
Skeletal survey and radiographs for lytic lesions	Screening phase for all subjects. Treatment phase: Assessment was repeated only if indicated based on symptoms	As indicated based on symptoms
Assessment of extramedullary plasmacytomas (radiology [CT or MRI] or physical examination)	Screening phase if plasmacytomas were known or suspected Treatment phase: Assessment was repeated only for subjects with plasmacytomas diagnosed at baseline. In such a case, assessments were performed every 6 weeks during the 24-week treatment phase and at the end-of-treatment visit.	Performed if extramedullary plasmacytomas were diagnosed at baseline. Every 8 weeks until development of PD.

CR=complete response; CT=computed tomography; IF=immunofixation; Ig=immunoglobulin; M-protein=monoclonal protein; MRI=magnetic resonance imaging; PD=progressive disease.

Patient population

The intention to treat (ITT) population comprised 222 patients from 53 study centres in 10 countries located in Eastern Europe, Western Europe, Argentina and India. Patients were randomly assigned to one of two treatment groups at a 2:1 ratio (n = 148 in the SC

group and n = 74 in the IV group). The majority of patients (91%) were enrolled in European sites.

Demographic and baseline characteristics for the patients were, in general, well balanced between the two treatment groups, with the exception of region, sex and performance status (PS): the SC treatment group had 50% males whereas the IV treatment group had 64% males; a higher percentage of patients was enrolled in Western Europe in the IV treatment group (41%) compared to the SC treatment group (29%); and the median Karnovsky PS (KPS) score at baseline was 80 in the SC treatment group and 90 in the IV treatment group.

It is worth commenting that the stratification factors, that is, the number of lines of prior therapy and the ISS Stage, were well balanced. Some factors have prognostic relevance in myeloma and the SC treatment group had a higher percentage of patients with negative characteristics (that is, lower KPS, immunoglobulin A (IgA) myelomas, lytic bone lesions, and impaired renal function), with the exception of high risk cytogenetics, which were higher in the IV treatment group.

In the ITT population, one patient in the SC treatment group was randomised but not treated. Of the 147 treated patients in the SC group, 81 (55%) completed Cycles 1-8 of treatment, 42 (28%) discontinued treatment and 18 (12%) received 9-10 cycles of treatment. Of the 74 treated patients in the IV treatment group, 39 (53%) completed Cycles 1-8 of treatment, 24 (32%) discontinued treatment and 9 (12%) received 9-10 cycles of treatment. Some 21% of patients in the SC treatment group and 24% of patients in the IV treatment group discontinued therapy due to adverse events (AEs).

For the safety population, 147 patients in the SC treatment group and 74 in the IV treatment group received at least one dose of study medication. The median number of cycles administered was 8 for both treatment groups. The median time of treatment was 22.57 weeks for both groups.

Exposure

In the SC treatment group the median dose intensity for bortezomib in the first 4 cycles was 5.13 mg/m²/cycle, indicating a relative dose intensity of 0.987. Median dose intensity for Cycle 5 and higher was 4.88 mg/m²/cycle indicating a relative dose intensity of 0.938. In the IV treatment group, the median dose intensity for bortezomib in the first 4 cycles was 4.89 mg/m²/cycle, indicating a relative dose intensity of 0.94, and the median dose intensity for Cycle 5 and higher was 4.91 mg/m²/cycle, with a relative dose intensity of 0.944.

Results

Primary endpoint

The ORR was 42% in both arms of study. The ORR after 4 cycles in the IV treatment group in this study was consistent with that observed in historical studies of single agent bortezomib in multiple myeloma studies. The 95% CI for the difference in the ORR between the SC and IV groups (0.6) was 6.1, 27.1, where the lower bound was above 0 and the p value for the non-inferiority hypothesis was 0.00201. This confirms non-inferiority of SC compared with IV administration. The stratified Mantel-Haenszel estimate of the relative risk (RR) of achieving a response for SC versus IV was 0.99, with 95% CI 0.71, 1.37, which excludes the pre-specified non-inferiority margin of 0.6.

Secondary endpoints

After 4 cycles of single agent bortezomib, 9 (6%) patients in the SC group and 6 (8%) in the IV treatment group had achieved CR; 9 (6%) in the SC group and 4 in the IV group had nCR; and 6 in the SC and 2 in the IV group had a VGPR. Therefore 24 (17%) patients in the

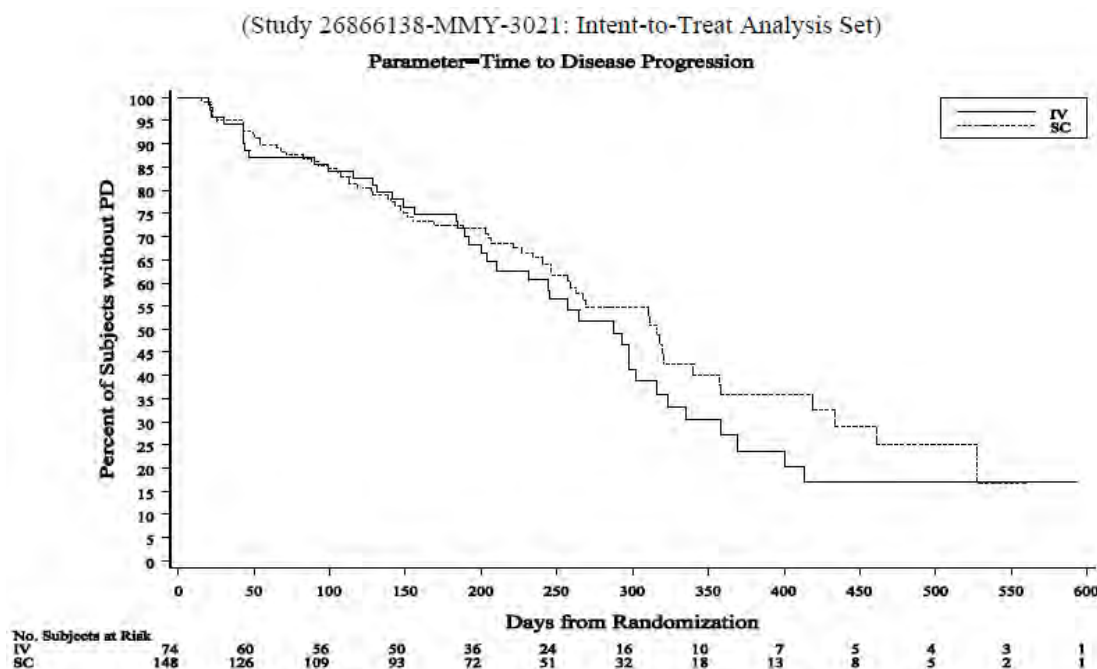
SC treatment group and 12 (16%) in the IV treatment group had best response of at least VGPR after 4 cycles.

The ORR after 8 cycles was 52% in both treatment groups and a stratified Mantel–Haenszel estimate of the RR of achieving a response for the two treatment groups was 1.00, with a 95% CI of 0.77, 1.31. Further, 36 (25%) patients in the SC treatment group and 18 (25%) in the IV treatment group had best response of at least VGPR after 8 cycles.

For time to disease progression in the ITT population, there were a total of 105 events: 64 (or 43.2% of subjects) in the SC group and 41 (55.4% of patients) in the IV treatment group. The median time to disease progression was 316 days (10.4 months) in the SC treatment group and 287 days (9.4 months) in the IV treatment group. The hazard ratio (HR) was 0.839 and the p value was 0.386 by stratified log-rank test. These results indicate that the time to tumour progression was similar for the two treatment groups.

Figure 2 presents a Kaplan-Meier plot of time to disease progression for the ITT population (censored for subsequent therapy):

Figure 2. Kaplan-Meier plot of time to disease progression



For PFS in the ITT population, a total 130 events were observed: 82 in the SC group and 48 in the IV group. The mean PFS was 310 days (10.2 months) in the SC treatment group and 245 days (8 months) in the IV treatment group. The HR was 0.824 and the p value was 0.294 by stratified log-rank test.

For overall survival and one year survival rate in the ITT population, a total of 59 deaths were observed, of whom 41 were in the SC group and 18 were in the IV treatment group. After a median follow-up of 11.8 months, survival data was not yet mature, with only 27% of events observed. At the clinical cut-off date of 31 August 2010, median survival was 21.5 months in the IV group and was not yet reached in the SC group. The median estimates were not considered reliable but the one year survival rate was 72.6% for the SC group and 76.7 % in the IV treatment group. The p value for the difference in one year survival rate was 0.503, indicating no difference in one year survival rate between the two treatment groups.

Based on Kaplan-Meier estimates, the median time to first response was 3.5 months for both treatment groups, with a HR of 1.059 and p value 0.772. For responders, the median

time to first response was 1.4 months for both treatment groups. The median time to best response was 106 days in the SC treatment group and 128 days in the IV treatment group, with a HR of 1.049 and a p value 0.807.

For responders in the response evaluable population, the median duration of response was 9.7 months in the SC group and 8.7 months in the IV group. The duration of response was censored for 45 subjects in the SC group and 20 in the IV treatment group who responded and subsequently progressed or relapsed from CR.

Exploratory analyses involved evaluation of best M-protein response. Changes in M-protein values are an indication of response and progression in the assessment of myeloma. Some 26% of patients in the SC treatment group and 27% in the IV treatment group had a 100% reduction of M-protein in the urine, and 31% of patients in the SC treatment group versus 27% in the IV treatment group had $\geq 90\%$ reduction.

For the effect of dexamethasone exposure and improving response from the end of Cycle 4 to Cycle 8: 82 patients in the SC treatment group and 39 in the IV treatment group received dexamethasone starting at Cycle 5. Results indicated that the addition of dexamethasone to bortezomib increased the response rate, and the improvement in response is similar for the two treatment groups.

Sub-group analyses of the ORR after 4 cycles involved assessment, staging, number of prior lines of therapy, sex, age, region, cytogenetics, dexamethasone exposure, prior transplantation therapy, prior thalidomide exposure, prior lenalidomide exposure, and prior imide exposure. Results were generally consistent across all the sub-groups.

Evaluator's comment: These data from a reasonable sized study have indicated that the primary objective was achieved, that is, demonstrating non-inferior in the ORR after 4 cycles in patients receiving bortezomib by either a SC or IV route. Apart from the equivalence in the ORR for the two treatment groups, other analyses were also comparable, confirming non-inferiority for the SC versus IV routes.

Supportive Study CAN-1004

Design

A supportive study, CAN-1004, is an open-label, randomised, Phase I study of patients with symptomatic multiple myeloma after at least one prior therapy. Patients were randomised without stratification to receive bortezomib as either a SC or IV injection. Bortezomib, at a concentration of 1 mg/mL, was administered at a dose of 1.3 mg/m² twice weekly for two weeks, followed by a 10 day rest period without treatment, for up to 8 cycles. Dexamethasone could be added after 2 cycles for patients with stable disease.

Objectives

The primary objective of the study was to characterise the PK and PD of the SC and IV routes of administration. Secondary objectives included determination of ORR and other efficacy parameters, including time to initial response, time to disease progression, time to tumour progression, and time to response.

Response evaluation performed by the investigator was based on EBMT criteria; evaluations were done after every cycle and at the end of treatment.

Patient population

A total of 24 patients from three study centres in France were randomly assigned to one of two treatment groups in a 1:1 ratio, with 12 patients being randomised to SC and 12 to IV routes. Demographic and baseline characteristics were comparable between the two treatment groups, with a mean age of 60.4 years (18/24 patients or 75% were < 65 years). There was no difference in age between the two treatment groups. A total of 42% of

patients were men and 58% women; 17/24 patients (71%) had an Eastern Cooperative Oncology Group (ECOG) PS score 0 and 7/24 had ECOG PS score of 1, with the distribution being similar between the two treatment groups. All patients had received at least one prior treatment for multiple myeloma: 10/24 patients or 42% received one prior treatment and five received at least two prior treatments.

Exposure

The median number of treatment cycles was 6 in both groups and the median total dose administered per patient was 24.25 mg/m² in the SC treatment group and 28.55 mg/m² in the IV treatment group.

Results

The best ORR in the ITT population, which includes all randomised patients, was 58% for the SC group versus 42% for the IV group.

The median time to tumour progression by Kaplan-Meier estimate was not estimable for the SC group and was 7.4 months for the IV treatment group. The HR was 0.804, 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. Up to a median time point of 6.6 months, no deaths were reported in either treatment group.

Evaluator's comment: In this small study, the data have confirmed the non-inferiority of SC administration compared to IV administration of bortezomib, thereby supporting the results from the pivotal trial.

Safety

Safety data from the two studies provided in this submission, namely the pivotal Study MMY-3021 and the supportive Study CAN-1004, are the principal data for assessments in relation to safety undertaken in this evaluation.

In the pivotal trial, the safety population included all randomised patients who received at least one dose of study drug. Of the 222 patients enrolled, 221 received treatment, which comprised 147 patients in the SC group and 74 in the IV group.

Adverse events were assessed on Day 1 of each cycle, with the appropriate screenings and evaluations including haematology, blood chemistry and assessment of vital signs. Electrocardiogram (ECG) and chest X-rays were undertaken as appropriate.

The safety population for the supportive Study CAN-1004 were again all randomised patients who received at least one dose of study drug, and comprised 12 patients in the SC treatment group and 12 in the IV group. Safety evaluations were conducted in a similar manner to the pivotal trial.

Adverse event data at various timepoints from these two studies were also compared to corresponding data from pooled historical studies with IV bortezomib administered at the same dose as that for the two principal trials, namely 1.3 mg/m². There were a total of 8 integrated historical IV studies included in the safety population of 1356 subjects.

Adverse events were reported according to National Cancer Institute (NCI) toxicity grades and criteria. It is worth commenting that an analysis of SC bortezomib local injection tolerability was also undertaken in Studies MMY-3021 and CAN-1004.

Study design and patient demographics for Studies MMY-3021 and CAN-1004 have been described in the *Efficacy* section, above.

Exposure

The median number of bortezomib cycles administered was the same for both treatment groups at 8, with a range of 1-10. In the SC and IV treatment groups, 79% and 77% of patients, respectively, received at least 4 cycles of treatment. In the SC group the percentage of patients receiving 5 cycles was 70%, versus 66% in the IV treatment group; the percentage of patients receiving 8 cycles was 56% and 51% respectively.

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

The median duration of bortezomib treatment was the same for both treatment groups, being 22.57 weeks and 22.29 weeks, respectively for the SC and IV groups. The median cumulative dose for all cycles administered was 32.55 mg/m² in the SC group, which was higher than the 31.20 mg/m² for the IV treatment group.

The median dose intensity of bortezomib in the SC group was similar to the IV group, being 4.84 mg/m²/cycle versus 4.78 mg/m²/cycle, respectively. The median dose intensities in Cycles 1-4 for the two groups were 5.12 mg/m²/cycle and 4.9 mg/m²/cycle. In Cycle 5 and beyond the median dose intensity was 4.81 mg/m²/cycle and 4.94 mg/m²/cycle, respectively.

Dose modifications

More patients in the IV treatment group than in the SC treatment groups had modifications. Some 34% of patients in the SC group had the Velcade dose reduced; of these 33% was due to an AE in the SC group, compared with 42% in the IV group. Doses were withheld in 31% of patients in the SC treatment group, of which 29% were due to an AE, compared with 40% in the IV treatment group, of which 34% were due to an AE. The percentage of patients with Velcade dose reductions in the first 4 cycles was the same in both groups (19%), whereas during Cycle 5 and beyond, fewer patients in the SC group compared with the IV group had dose reduction (31% versus 40%).

Doses were withheld for 25% of patients in the SC group, compared with 34% of the IV group, in the first 4 cycles, and for Cycle 5 and beyond the doses were withheld for 17% in the SC group versus 21% for the IV group.

Baseline characteristics

Baseline disease characteristics for the two principal treatment groups have been discussed in the *Efficacy* section, above. The baseline laboratory related characteristics and disease staging between the treatment groups were generally well-balanced. Patients in the SC group had a higher incidence of \geq Grade II haemoglobin decrease at baseline and a higher percentage of patients with impaired renal function (40% versus 30%).

Adverse events

Nearly all patients experienced at least one AE during the treatment period, being 95% for the SC group and 99% for the IV group. The incidence rate for bortezomib related AEs was also similar for the two groups, being 85% versus 92%. Overall, the incidence of \geq Grade III AEs was lower for the patients in the SC group (57%) compared to the IV group (71%).

Analysis by Grade showed there was a 12% difference between the SC and IV treatment groups for Grade III AEs (38% in the SC group versus 50% in the IV group), a 5% difference in the incidence of Grade V AEs (4% versus 9%), whereas Grade IV AEs were comparable between the two treatment groups (14% versus 12%).

In the SC treatment group, there was also a lower incidence of AEs leading to bortezomib discontinuation (22%, versus 30% in the IV group) and the incidence of serious AEs (SAEs) was similar between the two treatment groups (34% versus 36%).

Common AEs

Some 95% and 99% of patients in the SC and IV treatment groups, respectively, had AEs. Differences of at least 10% in the incidence of AEs by system organ class (SOC) indicated a higher incidence with IV versus SC treatment in the following classifications:

Gastrointestinal, Nervous system, Musculoskeletal and connective tissue, Respiratory and Mediastinal disorders. In comparison of AEs by preferred term, there was at least a 10% difference between the two groups in the incidence of diarrhoea (25% for SC versus 40% for IV) and peripheral sensory neuropathy (33% versus 44%), in favour of the SC treatment group. The only area where there is evidence of a difference favouring the IV treatment group was in relation to decreased weight, where 14% of patients in the SC group had a weight decrease, compared to 2% for the IV group. This is principally Grades I and II in severity. There is no Grade III weight decrease reported in the SC group.

In the analysis of most frequent ($\geq 2\%$ in either treatment group) \geq Grade III treatment emergent AEs, differences between the SC and IV treatment groups of $\geq 5\%$ were observed for Musculoskeletal and connective tissue disorders, Nervous systems disorders and Respiratory and Mediastinal disorders. Adverse events \geq Grade III severity by SOC occurred with highest frequency in Blood and lymphatic system disorders (33% in the SC group and 37% in the IV group), and most commonly included neutropenia (18% versus 22%) and thrombocytopenia (14% versus 20%). The incidence of Nervous system disorders was 14% versus 23% in the SC and IV groups, respectively, the most common being peripheral sensory neuropathy (4% versus 14%) and neuralgia (3% versus 8%).

Treatment-related AEs

In relation to treatment related AEs, 85% of the SC group and 92% of the IV group had a bortezomib related AE. Differences of $\geq 10\%$ in the SC treatment group compared with the IV group was found for Nervous system disorders (53% versus 63%) and Respiratory disorders (23% versus 14%). For all other systems the differences were $< 10\%$. The overall difference in treatment related Nervous system disorders were attributed to peripheral sensory neuropathy, being 33% for the SC group compared with 42% for the IV group. For Respiratory disorders, dyspnoea occurred less frequently in the SC group (1%) compared with the IV group (7%). Other differences in AEs between the SC and IV groups were found for asthenia (9% versus 20%) and diarrhoea (20% versus 30%), respectively.

Bortezomib related AEs \geq Grade III in severity are summarised in Table 9.

Table 9. Incidence of most frequent ($\geq 2\%$) Grade III or higher AE considered by the investigator to be related to treatment with Velcade.

(VELCADE Subcutaneous Integrated Summary of Safety (Studies MMY-3021 and CAN-1004): Pooled Safety Analysis Set)

System Organ Class Preferred Term	--- MMY3021 + CAN1004 ---	
	IV (N=86) n (%)	SC (N=159) n (%)
Total no. subjects with Grade ≥ 3 TEAE	49 (57)	64 (40)
Blood and lymphatic system disorders	29 (34)	36 (23)
Anaemia	4 (5)	9 (6)
Leukopenia	6 (7)	9 (6)
Neutropenia	19 (22)	21 (13)
Thrombocytopenia	15 (17)	15 (9)
Gastrointestinal disorders	3 (3)	6 (4)
Diarrhoea	3 (3)	1 (1)
Vomiting	0	3 (2)
General disorders and administration site conditions	7 (8)	8 (5)
Asthenia	4 (5)	1 (1)
Fatigue	3 (3)	3 (2)
Infections and infestations	2 (2)	7 (4)
Pneumonia	2 (2)	4 (3)
Nervous system disorders	17 (20)	20 (13)
Neuralgia	7 (8)	5 (3)
Peripheral motor neuropathy	2 (2)	1 (1)
Peripheral sensory neuropathy	11 (13)	7 (4)
Respiratory, thoracic and mediastinal disorders	3 (3)	1 (1)
Dyspnoea	2 (2)	0

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

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As indicated above, AEs \geq Grade III were more frequent in the IV group than in the SC group. A $> 5\%$ group difference was observed for Blood and lymphatic system disorders and Nervous system disorders. For Blood and lymphatic system disorders, 23% of patients in the SC group compared with 34% in the IV group had \geq Grade III events related to neutropenia (13% in the SC group versus 22% in the IV group) and thrombocytopenia (9% versus 17%). In relation to Nervous system disorders the differences were largely due to peripheral sensory neuropathy, being 4% versus 13%, and neuralgia, being 3% versus 8% in the SC and IV groups, respectively.

Deaths

The incidence of the deaths was similar for the two treatment groups. The incidence of treatment related deaths within 30 days after last study medication was low and the same for both treatment groups, being 1%.

Serious AEs

In relation to treatment-emergent serious AEs (SAEs), the overall incidence was similar for the two groups, being 34% versus 36%, except for administration site conditions where patients in the SC group had a 7% incidence of SAEs compared with 1% of the IV group.

The overall incidence of bortezomib related SAEs was similar in the two treatment groups, being 18% versus 17%. The only differences were in relation to diarrhoea (0% versus 2% in the SC and IV groups, respectively), pyrexia (2% versus 0%) and peripheral sensory neuropathy (1% versus 2%).

AEs leading to dose modification

Adverse events leading to a reduction in bortezomib dose occurred in 33% of the SC group compared to 42% of the IV group. The most frequent of these was related to Nervous system disorders, particularly peripheral sensory neuropathy (16% in the SC group versus 28% in the IV group) and neuralgia (10% versus 16%).

Adverse events leading to withholding of bortezomib dose occurred in 29% of patients in the SC group, versus 34% in the IV group. The most frequent reasons for this included neutropenia (7% in each group) and thrombocytopenia (3% in the SC group versus 7% in the IV group), whereas for Nervous system disorders, peripheral sensory neuropathy accounted for 3% versus 8%, and neuralgia accounted for 3% versus 7%, again favouring the SC group.

Adverse events leading to discontinuation of bortezomib occurred in 24% of patients in the SC group, compared with 30% in the IV group. The most frequent reasons were peripheral sensory neuropathy in 5% versus 12% and neuralgia in 4% versus 8%.

Adverse events of clinical relevance

Peripheral neuropathy

There was a 16% lower incidence of peripheral neuropathy (all grades) in the SC group compared with the IV group, being 40% in the SC group versus 56% in the IV group. For events of at \geq Grade II severity, the incidences were 25% versus 42%, whereas for events \geq Grade III in severity, these were 7% versus 16% in the SC and IV groups, respectively. The incidence of bortezomib discontinuation due to peripheral neuropathy was 7% lower for the SC group (7%) than for the IV group (14%).

The median cumulative dose for bortezomib to the first onset of any grade peripheral neuropathy was 37.9 mg/m² in the SC group and 22.3 mg/m² in the IV group, with an earlier onset of peripheral neuropathy for the IV group compared to the SC group.

The median cumulative dose of bortezomib at the first onset of \geq Grade II peripheral neuropathy was 36.2 mg/m² in the IV group but was not estimable for the SC group. At a cumulative dose of 20.8 mg/m² (corresponding to 4 cycles), the estimated event rate in the SC treatment group was 14.9%, compared to 28.9% in the IV group.

In relation to \geq Grade III peripheral neuropathy events, at a cumulative dose of 20.8 mg/m² the estimated event rate in the SC treatment group was 6.3%, compared with 13.1% in the IV group.

Cardiac disorders

The overall incidence of ventricular rhythm disorders was similar for the two treatment groups with no marked differences between the two treatment groups observed for any specific event. In relation to heart failure, the incidence of treatment emergent heart failure events was similar between the two treatment groups, being 2% versus 3% in the SC and IV groups, respectively.

Acute diffuse infiltrating pulmonary disease

Only one patient experienced such an event (described in the treatment emergent data) and this was in the SC treatment group. This event did not result in treatment discontinuation.

Herpes Zoster reactivation

The incidence of treatment emergent Herpes Zoster events was similar between the two treatment groups, being 11% in the SC group and 9% in the IV group, and most were considered related to bortezomib (8% versus 6%, respectively). It is noteworthy that in the pivotal study antiviral prophylaxis was administered to 46/147 patients in the SC

treatment group and to 30/74 patients in the IV treatment group. The incidence of Herpes Zoster reactivation was one subject in the SC treatment group and nil in the IV group, indicating effectiveness of such prophylaxis.

Local injection site tolerability

Of the 159 patients who received at least one SC injection, 96 (60%) of patients reported at least one injection site reaction, with 89 patients having a reaction at the first Cycle. Some 39% of the injections were associated with redness. It is noteworthy that reactions of redness appear to diminish over the course of the cycle with 47% of patients having reactions at Cycle 1, Day 1 and 34% of patients having reactions at Cycle 1, Day 11. All reactions resolved, with median time to resolution of 6 days (range 1-73 days). In the pivotal study, only two patients reported having severe local reactions, one being a case of pruritus and the other being a case of redness.

Clinical laboratory evaluations

The majority of patients in both treatment groups experienced Grade I or II haemoglobin changes during treatment, with a higher incidence of Grade II changes in the SC group (50%) than in the IV group (41%). The incidence of \geq Grade III changes in haematology parameters was lower for patients in the SC group compared to the IV group, with the exception of changes of at least Grade III haemoglobin which is similar for both treatment groups (10% and 11%). There was a 9% lower incidence of \geq Grade III neutropenia in the SC group (19%) versus the IV group (28%), and a 4% lower incidence of thrombocytopenia (18% versus 22%).

In relation to chemistry parameters, the overall incidence was generally low and similar for both treatment groups; the most common changes were in liver enzymes, hyperkalemia, hypokalemia, hypernatremia and hyponatremia. The incidence of these however was generally similar between the two treatment groups.

Vital signs

The only vital sign of note with changes related to treatment was weight loss, which was documented in 70% of patients in the SC group, versus 67% in the IV group. A maximum weight loss of 5-10% was reported in 21% of patients in the SC group, compared with 16% in the IV group. Weight loss between 10-20% was similar for both treatment groups, being 12% and 10%, respectively. A degree of weight loss \geq 20% was reported for one patient in the IV treatment group.

Adverse events in special populations

Assessments included a review of AEs in relation to age for patients aged $<$ 65 years and those aged \geq 65 years. In those aged \geq 65 years, there is a lower incidence of \geq Grade III AEs in the SC group (59%) than in the IV group (80%) and a lower rate of bortezomib discontinuations in the SC group (25%) than in the IV group (33%).

In relation to gender, the incidence of \geq Grade III events was lower in the SC group for both males (59%) and females (56%) than in the IV group (72% for males and 69% for females).

In relation to patients with impaired renal function (creatinine clearance \leq 60 mL/min) compared to patients with normal renal function, there were no major safety differences between the SC and IV treatment groups.

In relation to hepatic dysfunction, assessments were made on the basis of AEs in patients with baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $<$ 1.5 above normal. Patients with this criterion in the SC group had a lower incidence of \geq Grade 3 adverse event than those in the IV group (55% versus 70%) and also had a fewer discontinuations due to AEs (23% versus 30%).

Evaluator's comment: These data have essentially shown that the safety profile for SC bortezomib compared to IV bortezomib is generally similar. The only differences relate to a somewhat greater degree of Grade III events for the IV treated patients and in particular a greater incidence of peripheral sensory neuropathy associated with IV therapy. Thereby, the safety profile for SC administration is acceptable and, if anything, a slight improvement on that experienced with IV administration.

List of questions

The clinical evaluator did not raise any questions.

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The data provided from pivotal Study MMY-3021 show that it achieved its primary objective of demonstrating non-inferior in the ORR after 4 cycles for patients receiving bortezomib by either the SC or IV route of administration. The ORR after 4 cycles was 42% for both SC and IV treatment groups. The ORR after 4 cycles in the IV treatment group was consistent with that observed from historical studies of single agent IV bortezomib in multiple myeloma. The secondary measures of efficacy, including response after 8 cycles, time to response, duration of response, time to tumour progression and PFS, were also similar for the two routes of administration. Further, SC administration did not affect the additional efficacy benefit following addition of dexamethasone to the treatment regimen for patients with sub-optimal response to bortezomib monotherapy. Accordingly, the data from the pivotal study, together with the supportive data from Study CAN-1004, have shown that the potential benefits gained by bortezomib therapy were not diminished when treatment was undertaken by the SC route.

First round assessment of risks

The safety data provided from the combined analysis of the pivotal Study MMY-3021 and the supportive Study CAN-1004 indicate that, overall, the AE profile for SC administration of bortezomib is similar to, and of similar magnitude to, that observed with IV administration of bortezomib.

There were some differences, notably that AEs of \geq Grade III severity were less frequent among those patients receiving SC bortezomib (57% for SC versus 71% for IV). Further, AEs leading to treatment discontinuation also favoured the SC route of administration, with 22% for SC versus 30% for IV. Of particular note was the fact that the incidence of peripheral neuropathy was clearly less for those patients receiving SC bortezomib compared to the IV formulation. This was particularly noted for those patients with \geq Grade II peripheral neuropathy of the sensory type, being 24% for SC versus 41% for IV, and this is maintained when analysis of \geq Grade III sensory neuropathies were assessed (6% for SC versus 16% for IV). It is also appropriate to indicate that the safety data from the two randomised studies evaluated for this submission were consistent with that from the historical data, indicating that there were no major changes identified in these current studies.

Accordingly, it would appear appropriate to indicate that the relative risks associated with SC administration of bortezomib are at least equal to those observed with the IV formulation, and in some respects are improved.

It is worth commenting on local tolerance with SC administration and although approximately 60% of patients had a local reaction, in the vast majority of incidences this was mild to moderate in nature and generally comprised a redness of the area of administration. There was only one case of a Grade III reaction in the randomised studies.

First round assessment of benefit-risk balance

The data from the two submitted studies support the proposal that SC administration of bortezomib is associated with at least equivalent efficacy to that provided by IV administration in patients with previously treated multiple myeloma. Furthermore, the safety data provided from this evaluation also support the proposal that the SC formulation is not associated with any compromise to AEs and in particular appears to be superior to IV therapy in some areas.

Accordingly, the evaluator considers the benefit/risk balance for bortezomib is well maintained in favour of benefits for SC administration and supports the approval of Velcade for SC use.

First round recommendation regarding authorisation

The evaluator considered the data provided in this submission were sufficient to support registration of a new route of administration (SC injection) for bortezomib 3.5 mg powder for injection, in addition to the currently approved IV administration.

V. Pharmacovigilance findings

Risk management plan

The TGA's Office of Product Review (OPR) considered that a Risk Management Plan (RMP) was not required for this application.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections to registration on chemistry and quality grounds. The bioavailability data submitted with the application are discussed below (*Pharmacokinetics and Biopharmaceutics*).

Nonclinical

Studies comparing SC with IV administration were conducted in Cynomolgus monkeys. The two routes of administration resulted in comparable PD effects (20S proteasome inhibition), PK and toxicity. Local tolerance of SC administration was also studied in rabbits, using concentrations of injection up to 3.5 mg/mL. Histopathological changes were minimal.

There were no nonclinical objections to registration.

Clinical

The clinical evaluator has recommended approval of the application.

The submission included two clinical studies:

- Study CAN-1004; a small Phase I, randomised, open trial with two parallel groups comparing SC and IV administration in 24 subjects with relapsed myeloma; and
- Study MMY-3021; a large Phase III, randomised (2:1), open trial with two parallel groups comparing SC and IV administration in 222 subjects with relapsed myeloma. This trial has been published².

Pharmacokinetics and biopharmaceutics

In Study CAN-1004, SC administration was associated with a reduced C_{max} and AUC compared to IV administration on both Days 1 and 11. Formal bioequivalence could not be concluded.

In Study MMY-3021, PK data were available in a subgroup of patients ($n = 31$). On Day 11, C_{max} was again significantly lower following SC administration. However, AUC values were comparable and the evaluator concluded that bioequivalence had been established.

Pharmacodynamics

In both studies, SC administration was not associated with a reduced level of inhibition of 20S proteasome activity at Day 11.

Efficacy

Study MMY-3021: The main clinical efficacy data in the submission come from this Phase III study. The trial enrolled subjects with multiple myeloma whose disease had relapsed or progressed following 1-3 lines of prior systemic antineoplastic treatment. Subjects were not permitted to have received prior bortezomib.

Subjects ($n = 222$) were randomised (2:1) to receive either SC or IV bortezomib at a dose of 1.3 mg/m² on Days 1, 4, 8 and 11 of a 21 day cycle. Treatment was continued for up to 8 cycles. This dosage regimen is the same as that currently approved in Australia for IV use.

The primary endpoint was ORR after 4 cycles of treatment. The trial was designed as a non-inferiority study. Non-inferiority would be concluded if SC administration retained at least 60% of the efficacy of IV administration (that is, if the lower bound of the 95% CI for the difference between ORR_{SC} minus $(0.6 \times ORR_{IV})$ was greater than 0).

The ORR in both groups was 42%. The value for ORR_{SC} minus $(0.6 \times ORR_{IV})$ was 16.8% (95% CI: 6.1, 27.1). As the lower bound of the CI (6.1) was greater than 0, non-inferiority was concluded.

There were a variety of secondary endpoints measured. Results of these endpoints also suggested comparable efficacy between the two regimens.

Study CAN-1004: This study also enrolled patients with myeloma which had relapsed after at least one prior treatment. ORR was a secondary endpoint; ORR was 58% in the SC group and 42% in the IV group.

² Moreau P., Pylypenko H., Grosicki S. *et al.* Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol* 2011; 12:431-440.

Safety

A total of 159 subjects were treated with SC administration in the submitted studies. Median duration of treatment was 8 cycles.

A pooled analysis of safety was included in the submission. The incidence of AEs, SAEs, AEs \geq Grade 3 or discontinuations due to AEs was not increased with SC administration.

The pattern of individual AEs seen with SC injection was consistent with that previously observed for IV injection. The incidence of individual AEs was not increased in SC arms of the two studies. The data suggested that SC injection may be associated with a reduced incidence of peripheral neuropathy.

Approximately 60% of subjects had some degree of injection site reaction following SC injection. However most of these reactions were mild to moderate in severity and only one patient developed a Grade 3 injection site reaction. Only one subject discontinued SC treatment due to an injection site reaction.

Risk management plan

A RMP was not required to be submitted with the current application.

Risk-benefit analysis**Delegate considerations****Issues***Efficacy endpoint*

The pivotal study in the submission used ORR as the primary endpoint, and the basis for concluding non-inferiority. The EMA *Guideline On the Evaluation of Anticancer Medicinal Products in Man* (CPMP/EWP/205/95/Rev.3/Corr.) has been adopted by the TGA. This specifies that endpoints such as PFS or overall survival are the appropriate ones to use for oncology trials. Demonstration of non-inferiority using PFS or overall survival would have required a much larger trial. As the PK data suggested comparable systemic exposure with SC and IV injection, and no other changes are proposed to the dosage regimen or indications, the Delegate considers the use of ORR as the primary endpoint to be acceptable in this instance.

Product Information

The Delegate proposed to make several revisions to the PI. Details of these are beyond the scope of this AusPAR.

Proposed action

The data submitted suggest that SC injection results in comparable systemic exposure to that achieved with IV injection. The Phase III study also suggests comparable efficacy and safety. The Delegate therefore proposed to approve the application. The advice of the Committee was requested.

Response from Sponsor

The sponsor's response to the Delegate's overview contained only comments regarding proposed changes to the PI document. Details of these are beyond the scope of this AusPAR.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM agreed with the Delegate that the data submitted indicate that the SC injection results in comparable systemic exposure to that achieved with IV injection and that the Phase III study also suggests comparable efficacy and safety profiles. In addition, the ACPM considered the SC route of administration has the potential to improve the safety profile compared to the currently registered alternative IV route.

The ACPM agreed with the Delegate that the proposed amendments to the PI and Consumer Medicine Information (CMI) should include:

- a statement in the appropriate sections of the PI and CMI to more accurately reflect the lack of comprehensive data in patients with reduced renal function.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Velcade containing bortezomib 3.5 mg powder for injection vial for the new SC route of administration. The full indications remain unchanged and are:

Velcade, in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy.

Velcade, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.

Velcade is also indicated for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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Reference/Publication #